SKIN AND MUCOUS MEMBRANE *

R. M. B. MACKENNA
M.A., M.D. Cantab., F.R.C.P.
PHYSICIAN-IN-CHARGE OF THE SKIN DEPARTMENT, ST. BARTHOLOMEW'S HOSPITAL, LONDON, E.C.1

MANY advances in dermatology in the last 30 years have been due to the great increase in our knowledge of the biochemistry of the skin in health and in disease. Until early in this century the skin was regarded as an integumentary structure, having sebaceous and sweat glands, appendages (hair and nails), an efficient sensory nerve-supply, and a complex of arterioles, venules and lymphatics, with some other features of interest, such as the musculi arrectores pilorum. Keratohyalin and eleidin were noted and named during the last quarter of the 19th century (some of the early references are given in MacLeod's Practical Handbook of the Pathology of the Skin [1903]), and a study of the nature of these compounds was one of the first biochemical investigations in regard to the epidermis which attracted attention. During this century the realisation that biochemical investigation was important to the dermatologist received great impetus from Bloch's (1927) work on pigmentation, and from Lewis's (1927) observations on wealing and the release of H-substance.

Since those days we have learnt that a great number of very complex chemical activities are constantly proceeding in the epidermis and corium, and on the efficiency of these processes the health of the skin depends. When these activities are checked or become abnormal, signs of what we call disease may appear. Many of these activities depend on enzyme reactions.

For example, in urticaria relatively large amounts of histamine or acetylcholine are released, and the simplest explanation is that the wealing occurs merely because of some pathological process whereby an excess of either of these compounds is set free. But we are beginning to wonder whether in some instances, particularly in chronic cases with mild lesions rather than acute ones with extensive symptoms, the fault lies at least as much with an enzyme system, which should rapidly neutralise the excess of histamine or acetylcholine, as with the chemical system involved in the production of these compounds. To take another example, although the method of formation of psoriasis lesions remains an enigma, Roe (1959) has suggested —with good evidence to support her views—that psoriasis represents an error of sulphur metabolism in the epidermis whereby sulphate is built up into abnormal glycoprotein and is not available for the synthesis of sulphur-containing amino-acids and therefore of keratin itself. Now, clinically, lesions of psoriasis can arise on mucous membrane as well as on skin; hence if the lesions on the skin are due to changes or faults in the biochemical activities of that skin, then the lesions on mucuous membrane must be due to abnormalities in the chemical activities of the affected mucosæ.

We know a great deal about the chemical processes in the epidermis; but, at the moment, dermatological thought has stopped there, and, despite the work of Miles Taylor (1958), Yoffey (1958), and a few others, is not greatly interested in the biochemistry of mucous membrane. Mucosa is still regarded by most of us as a wonderfully adapted lining of many cavities; unlike the skin, it is relatively impervious to maceration by physiological fluids, and it excretes or secretes mucus. In some areas this lining membrane is a ciliated epithelium, but in others—such as the mouth and certain areas of the nasal cavity—histological photographs show much resemblance to the epidermis. On these areas occur the eruptions in which the dermatologist is interested. If we consider two facts—firstly that the lesions of certain skin-diseases which can attack mucosa also are, in the skin, due to biochemical abnormalities, and secondly that histologically in certain areas the mucosa has a cellular structure which has many similarities with epidermis—then I suggest that it is reasonable to postulate, in many mucosal areas, continual chemical processes which are possibly vital for the life of the individual and certainly vital for the health of the mucosa itself, of which we know little or nothing.

On the plane of physical structure as opposed to chemical activity, recent dermatological work may have a bearing on mucosal function.

Thus Mali (1956) studied the mechanism of water transport through the epidermis, and demonstrated a barrier zone situated between the cells of the prickle-cell layer (stratum spinosum) and the horny layer (stratum corneum). Hitherto almost unsuspected, despite earlier work by Derksen et al. (1937), this zone determines the small inward and outward permeability of the epidermis for water vapour. Little is known about its structure, but it may comprise a tight network of young keratin fibres between which fatty and other substances are found. Possibly this barrier has cellular or other components. Yoffey (1958) has made observations on the passage of fluid and other substances through the nasal mucosa; but does a homologous or analogous barrier exist in certain areas of nasal, and in most areas of oral, mucous membrane?

Two other matters, entirely different in theme, may provoke thought if one carries over these somewhat philosophical concepts of the skin to mucous membrane.

Goldsmith (1936) summarised the first very cogently. The glands of the skin were differentiated by Ranvier into two types—holocrine and merocrine. In a holocrine gland the secretion entails and is formed by complete disintegration of the gland cells; this, for example, happens when sebum is formed in the sebaceous glands. In the epidermis the cells of the stratum germinativum constantly multiply; and as they multiply they degenerate and are extruded to the surface. During this process they produce a wax-like substance (keratohyaline→eleidin→horn fat), and the remains of the cells are transformed into horn, of which the chief component is keratin.

Commonly we regard the outermost layer of horn cells as little more than detritus on the surface of the skin. But, regarded in the way that Goldsmith describes, they are among the most highly elaborated cells in the body. Further—and more important—the whole epidermis of the human body can be regarded as a relatively vast gland which, unlike most other glands, is widely open to the air, and is engaged minute by minute in life, and possibly for a short while after death, in producing horn fat and horn.

The Concept of Symbrosis

Pinkus (1958) has applied the concept of symbiosis to normal and abnormal growth in the human epidermis.

It is believed that in human skin the melanocytes (which are present also in olfactory mucosa) are formed in embryo

* A lecture, given under the title "The Dermatological Aspect of Certain Diseases of the Mouth and Ear", to the Royal College of Surgeons of England and the Institute of Laryngology and Otology on March 3, 1960.

from the neural crest and migrate to the epidermis through the mesenchyme, coming to rest at the dermoepidermal junction. They live, therefore, in close association with the cells of the malpighian layers; hence we have in this situation two types of genetically independent cells, with very different biological, biochemical, and genetic characteristics, living in symbiosis. They are so distinct that during the period of forced epidermal proliferation after stripping with plastic tape the malpighian cells undergo rapid proliferation whilst the melanocytes remain almost quiescent. The human melanocyte is therefore to be regarded as a symbiont in the epidermis and also in mucous membrane. Benign neoplasia of melanocytes leads to the formation of cellular nævi; but if the symbiosis really breaks down and if perhaps other factors come into operation malignant melanoma results, the melanocytes having ceased to be symbionts and having become parasites.

Other work which Pinkus (1958) discusses indicates that the walls of the hair follicles and those of the eccrine sweat ducts are to be regarded as individual components of the epidermis, living their own lives within its substance; they have, and in health they maintain, their own individuality. They live in symbiosis with the rest of the epidermis. If the skin is sandpapered or planed the sweat ducts regenerate before the wound becomes re-epithelialised. The hair follicles also reconstitute their ostia, and if these and the surrounding epidermis are destroyed they divert some of their energy to the formation of new epidermis—a fact which has been known for a long time, for the surgical textbooks of our student days stated that in the operation of rhinophyma the surgeon should not be afraid of removing a great deal of the hypertrophic tissue, as epithelium regenerated readily from the remnants of the sebaceous glands.

This new concept of two units in the skin retaining their own biological entity is very important in regard to cancer. Here I leave Pinkus for the moment and interpolate something of my own, based on his work, but highly speculative. Some workers believe that all basal-cell carcinomata arise from pilosebaceous structures, and much advanced histopathology has been written about the development of basal-cell masses, and the tendency sometimes noted in what have been called "adnexal carcinomata" for these masses to resemble hair-follicle or sebaceous-gland structure. In fact the accessory structural similarities are such that Foot (1947) is cited by Sutton (1956) as confirming the earlier work by recognising the analogy of basal-cell tumour development to pilar, sebaceous, and sweat units, with variations in differentiation. Perhaps in all basal-cell carcinomata the symbiosis between the normal epidermis and a sudiferous duct breaks downs: the duct becomes parasitic on the epidermis and basal-cell carcinoma develops. But if the reverse happens—the cells of the malpighian layer losing their symbiosis with the sweat and pilosebaceous ducts in their midst and becoming parasitic on them—then that is the beginning of true metastasising cancer.

In a later paper, and one which is very difficult to follow, Pinkus (1959) suggests that basal-cell carcinoma (rodent ulcer) differs from squamous-cell carcinoma in that proliferating squamous cells have no regard to their stroma except to invade it, whereas the proliferating basal cells remain within a mesodermal stroma and therefore do not metastasise.

Another matter in Pinkus' earlier paper (1958) deserves attention, to wit a discussion on precanceroses. These lesions must also arise in structures other than the skin and mucosa: rectal surgeons and gynæcologists know much about them, and many general physicians and surgeons would like to know more. But one of the features of a precancerosis is that it may be visible if it can be approached by viewing instruments or the naked eye, although it does not cause any important symptoms. The cutaneous lesion known as keratosis senilis is closely related to the keratoses produced by X-rays or carcinogenic drugs, such as arsenic. Basically the lesions are degenerative precancerous keratoses produced by actinic rays. The affected epidermis apparently becomes incompatible and is treated as foreign by the adnexal epithelium of pilosebaceous ducts. The latter tries to cover the former; and, in doing this, thickens and becomes hyperkeratotic. Normal symbiosis is replaced by an uneasy balance in a struggle for survival between the epithelial systems.

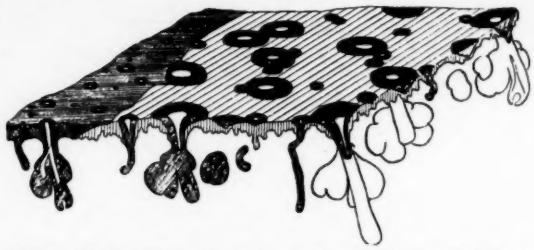


Diagram by Dr. H. Pinkus to illustrate cellular proliferation in keratosis senilis.

On the left the skin is normal; on the right the changes described in the text are depicted.

(From *Dermatologica, Basle*, 1958, **117**, 369.)

The figure (from Pinkus) shows that the epidermis is anaplastic with atypical budding: biologically it has become incompetent. The adnexal epithelium is hypertrophic, spreading peripherally from the duct orifices and attempting to cover and replace the incompetent epidermis. A stage later the adnexal epithelium may become confluent, entirely covering the anaplastic epithelium, which may then start growing downwards on the outside of hair follicles and sweat-ducts. Freudenthal (1926) described this alternation of parakeratotic and hyperkeratotic "columns" 34 years ago, although he did not know of the dynamic relation between the two types of epithelium. Whilst the epithelium from the adnexal ostia is normal, the epithelium which it covers is anaplastic. Statistics are not readily available, but squamous-cell carcinoma may arise in about 25% of these lesions.

In Bowen's precancerous dermatosis which has been called "the prototype of all carcinomata in situ" similar changes are described (Pinkus 1958). Watkyn-Thomas (1955) has stated that carcinoma in situ has been recognised in the larynx, and I believe it also arises in the mouth. One therefore may ask whether Pinkus's concept of symbiosis can be applied to explain the genesis of certain malignant changes in mucosæ.

As a dermatologist I must make brief reference to keratoacanthoma, the lesion which so often in the past was diagnosed as epithelioma. It was hoped that study of this self-limiting and self-curing tumour would increase our knowledge of carcinomata. The lesion can appear on the outer ear, and certainly it may involve the lip. Whether it can start in the vermilion border of the lip, or whether it always arises in the adjacent skin and then involves that border is disputed, but at St. Bartholomew's Hospital we have seen a case in which the tumour (diagnosed clinically and histologically) was confined to the vermilion border. It seems unlikely that keratoacanthoma can develop in the mouth or nose; but until we really know whether this lesion arises because of infection or because of neoplastic change it is not worth further consideration in the present context.

So-called Diseases of the Skin which involve Mucosa

It would be fair to define diseases of the skin as those in which the complex of signs and symptoms are chiefly seen in that organ, but there is no adequate definition. Syphilis, tuberculosis, leprosy, and other systemic disease have phases in which, under this definition, they are dermatological maladies, but most dermatologists in this

country have renounced the devil and all his works by ceasing to deal with venereal diseases; we still are happy to treat cutaneous tuberculosis, but leprosy now has its own specialists. Otherwise we largely treat those ills, however systemic they be, which were treated as " diseases of the skin " by our predecessors, and by tradition (though we are sometimes asked to help in diagnosis but never in treatment) we eschew zymotic diseases. Somewhat irrationally we take within our purview a selected group of abnormalities and diseases of the mouth, and more logically we share an interest in the nasal vestibules and outer ears.

Lichen Planus and Psoriasis

Shellow (1958) has described the cutaneous maladies in which the mouth might be involved. His paper is a classic and I refer to it because it strengthens my argument concerning the homologies between skin and oral mucosa.

The lesions of lichen planus have been seen on all accessible mucous membranes of the body (Darling and Crabb 1955). The oral manifestations have been excellently described by Cooke (1954). Oral lesions may precede, follow, or appear at the same time as skin lesions, and we all know of cases in which the malady seems to be confined to the mucosæ. Thomson (1928) reported a case with lesions on the tonsils and skin, but none on the buccal or lingual mucosæ. The lips, and particularly the lower one, may be involved. Lichen verrucosus —a variant of lichen planus—is not associated with thick and warty lesions in the mouth resembling those on the skin; Darling and Crabb report that in this malady the oral lesions are lace-like or striated in pattern. Whilst diagnosis can usually be clinched by biopsy, the histopathologist sometimes finds accurate interpretation of the material difficult. Carcinomatous degeneration of mucosal lesions is rare, but Warin et al. (1958) reported that, in forty-five cases of lichen planus, the oral lesions ulcerated in thirty and epithelioma developed in two.

The ætiology of lichen planus and also of psoriasis (which we will now consider) in unknown. Very occasionally the buccal mucosa is involved in psoriasis, but according to Shellow (1958) the skin is always involved too.

On the mucosa the epithelium thickens and desquamates, and the appearance of the lesions change in the same way as those in the skin—sometimes being thick and scaly, and sometimes just erythematous. The superior and inferior surfaces and the sides of the tongue may be involved (Usher 1933), and lesions have been seen on the hard and soft palates (Norrino and Yaffee 1957). The vermilion parts of the lips are more often affected by psoriasis than is the oral mucosa. In acute cases, particularly of the guttate generalised type, diffuse or patchy white-yellow scaling may be noted, often complicated by fissuring. Chronic psoriasis may be accompanied by isolated patches or more diffuse scaling of the lips. An almost constant feature is that when the skin eruption fades the mucosa resumes its normal appearance.

Though most textbooks do not give the information, it seems to be accepted that in about one case of pityriasis rosea in three hundred the oral mucosa on the cheeks and sometimes on the palate may be involved. We do not know the ætiology of pityriasis rosea but it is a relatively trivial disorder (though it often alarms the patient considerably) which usually persists only for a few weeks. (For details and references, see Shellow [1958].) Here again, the mucosæ become normal when the skin eruption clears.

Skin-diseases with Oral Lesions

So-called skin-diseases in which oral lesions may be found are: epidermolysis bullosa, keratosis follicularis or Darier's disease (in which the œsophagus may sometimes be involved [Brunauer 1925]), pityriasis rubra pilaris, pityriasis lichenoides et varioliformis acuta, lichen sclerosus et atrophicus, urticaria pigmentosa, and acanthosis nigricans (in which the tongue and other oral areas may be involved, pigmention occurring in 50% of cases [Grace and Schwartz 1934]). But I have left out a group of maladies, one proved and the others possibly due to virus infections—namely, erythema multiforme (including Stevens-Johnson syndrome), Reiter's syndrome, aphthosis (including Behçet's malady), and pemphigus.

The first, erythema multiforme, I will omit. In twenty-three cases of Reiter's syndrome Hall and Finegold (1953) found that lesions in the mouth (which comprise vesicles surrounded by an erythematous areola, the vesicles rupturing early, and their bases being then covered with a grey-white membrane) were the most frequent eruptive signs, the palate and buccal mucosa being involved in 48%, some also having lesions on the tongue.

Pemphigus and Pemphigoid

Lever of Boston, Massachusetts, in a paper (1953) entitled Pemphigus, by blending observations made at Harvard and the Massachusetts General Hospital with much carefully selected data from international sources (particularly from the French school, and including Civatte's historic contribution [1943]) was able to produce order in a chaos of confused opinion. Of course many of his views have been attacked, but they have withstood very well the criticism of the last 4 years.

True pemphigus is characterised by a specific histological picture: fundamentally there are only two forms—pemphigus vulgaris malignus and pemphigus foliaceus. Pemphigus vegetans (hitherto often considered an allied but separate malady) is a variant of pemphigus vulgaris malignus, modified because the patient has a higher resistance to the disease (Director 1952), and pemphigus erythematosus (the so-called Senear-Usher syndrome) is an early phase or abortive form of pemphigus foliaceus, or possibly of pemphigus vulgaris. All varieties of true pemphigus should be regarded as lethal diseases, with the caveat that in pemphigus erythematosus the patient's resistance may overcome the malady.

Lever further simplified the existing confusion in regard to so-called bullous diseases, by taking the word " pemphigoid " which, since the days of Hippocrates, had been rambling round in medical literature usually in the guise of an adjective, and giving it the significant status of a noun. Pemphigoid, Lever suggested, should be used for certain bullous eruptions which have a non-specific histological picture, which are not lethal, and which include two types—bullous pemphigoid (? bullous dermatitis herpetiformis) and benign mucous membrane pemphigoid. Certain critics dislike the name bullous pemphigoid rightly, I think, for it is tautological, whilst others deplore the omission of familial benign chronic pemphigus from the classification. Lever safeguarded himself, however, in this last regard by suggesting that until more was known about that rare malady it should be regarded as an independent entity.

Rook and Waddington (1953) took matters a little further and emphasised that pemphigoid differs from pemphigus in its clinical features, course, prognosis, and response to treatment; further they clearly stated their belief that the pathological process is fundamentally different from that of pemphigus. Recently, Gibb (1955) accepted Lever's (1953) work, and emphasised that pemphigus vulgaris malignus and benign mucosal pemphigoid are of major interest to laryngologists, for, on Lever's figures, lesions are seen in the mouth and throat in nearly all cases of pemphigus vulgaris, and in 90% of mucosal pemphigoid, but only in 7% of pemphigus foliaceus, and 34% of bullous pemphigoid; moreover primary oral lesions are

extremely rare in pemphigus foliaceus and in bullous pemphigoid. Although her evidence for making the suggestion is vulnerable, Curth (1955) has suggested that a genetic factor may operate in mucosal pemphigoid since a significantly greater number of patients seem to be born in the British Isles than elsewhere.

Clinically if we follow Rook and Waddington (1953) the sex-ratio in pemphigus vulgaris is three males/one female; the malady affects people aged between 50–70 years, the initial lesion is most commonly on the scalp or mucosæ, and mucosal involvement is frequent and early. Pemphigoid is a malady of an older age-group (53% are over 70), the sex incidence is equal, and except in mucosal pemphigoid the initial lesion is less frequently on the mucosæ than on the legs, arms, head, or trunk; the cutaneous lesions may in fact precede the mucosal involvement by several years (Gibb 1958).

Pemphigus is fatal; pemphigoid is relatively benign. It used to be taught that if the first lesions of pemphigus were in the mouth the prognosis was more grave than when they were in the skin. I believe we can regard this as an interesting paradox, for the observation was and is quite true, but the deduction is no longer valid. It arose because formerly the non-lethal malady we now call bullous pemphigoid was regarded as pemphigus vulgaris, and bullous pemphigoid usually starts in the skin, whereas pemphigus vulgaris starts in the mouth in many cases (55% according to Costello et al. [1957]).

When one examines cases of pemphigus or pemphigoid one seldom finds a blister on the mucosæ. The patients may say "I had a blister", but then often gives apparently valid evidence about a dental operation, or taking a too-hot drink, or a scratch from a (red-herring) bone, which, if one is not alert, may put the possible diagnosis of pemphigus entirely from one's mind. In pemphigus vulgaris, at the first examination, the laryngologist will usually find only few superficial painful erosions. Gibb (1958) as an otolaryngologist emphasised these points: increased salivation; painful swallowing due to pharyngeal involvement which may be so severe that there is dribbling of bloodstained saliva; hoarseness from laryngeal involvement; bloodstained nasal discharge if the nose is affected; and erosions which show little or no tendency to heal.

Mucosal pemphigoid attacks the eyes, the mucosæ of the mouth, nose and larynx, the œsophagus, and the genital and, sometimes, the anal mucosæ.

According to Church and Sneddon (1953) the sex-incidence varies from the other form of pemphigoid because females predominate (in their series of seven cases by six/one). Although lesions in the mouth are at least as common as conjunctival lesions, the malady is seldom diagnosed until it attacks the conjunctivæ—which is why it is still generally known as ocular pemphigus or ocular pemphigoid, and has been recognised for many years as a cause of blindness. Some workers insist that skin lesions are concurrent or may precede mucosal lesions by several years; this is not generally appreciated, and one school of thought desires to separate mucosal pemphigoid entirely from pemphigus and pemphigoid because of its predilection for mucosæ, and because of the very different sequelæ from the adhesions which it causes. In the mouth the lesions tend to be painless; the patient usually shows indolent denuded erosions which heal slowly, forming white scars. The scarring may result in adhesions, which sometimes form between the buccal mucosa and alveolus, obliterating the buccal sulcus. Some times the mucosæ of the soft palate, pillars of the fauces, and uvula are involved. Hoarseness may result from laryngeal adhesions. Fibrous stricture of the œsophagus is a rare complication, and usually the disease is not fatal unless œsophageal stenosis is severe. Corticosteroids have a good effect on active erosions, but none on adhesions and strictures.

So far as dermatologists and otolaryngologists are concerned, diagnosis must depend on histological examination. For this the so-called Tzanck test (Tzanck et al. 1954)—for which one merely takes a scraping from the floor of a bulla, and spreads it on a slide, where it is fixed, stained with a routine Giemsa stain, and then examined microscopically—is of great importance. In true pemphigus the lesions are intraepithelial; the intercellular bridges of the malpighian cells have disappeared so that a specific feature known as acantholysis is seen, and the cells themselves show distinct degenerative changes, with a relatively large nucleus and condensation of their cytoplasm at the periphery. In pemphigoid the blisters are formed below the level of the epithelium; as they enlarge they may encroach on the epidermis, but primarily they are subepithelial. This statement has been disputed but is generally accepted. These essential differences are beautifully shown by two illustrations in Gibb's paper (1958), and Lever (1953) has a good photograph of oral mucosa in mucosal pemphigoid.

Thus, in true pemphigus we have an epithelial lesion: in pemphigoid (and in some other blistering maladies—dermatitis herpetiformis, for example) a subepithelial one. Yet pemphigus is the lethal disease: pemphigoid and dermatitis herpetiformis are non-lethal. These facts can be used again to emphasise the point I have already made of the importance of cutaneous and mucosal epithelium in the life of the individual; the cogency of the observation is enhanced by Borrie's (1958) cryptic remark that, in pemphigus, whilst the sites of attack are the skin and mucosæ, the many postmortem changes which have been described in the central nervous system and visceræ are equally well seen after death in any chronic wasting disease.

Everyone is agreed that we do not know the cause of pemphigus: pemphigoid may often be a disease sui generis. Possibly (I think improbably) there is a genetic factor in mucosal pemphigoid in some instances (Curth 1955). Pemphigoid lesions can develop as a drug reaction which I have seen particularly after the use of organic arsenical compounds. Both in pemphigus and in pemphigoid any cellular infiltrate mostly comprises eosinophils, and there is no predominant invasion with the ubiquitous lymphocyte, a cell which perhaps carries immunological information (Burnet 1959). Ætiological theories concerning virus and bacterial infection, toxins, and salt retention have all been proposed and opposed without any significant facts emerging. Cohen et al. (1958) have produced a small amount of evidence to suggest adrenocortical dysfunction in the early stage of pemphigus vulgaris: possibly this can be linked with earlier work (discussed by Lever (1953) in which salt retention was considered to be a cause of the malady.

The observations by Peters et al. (1946) on vesiculation caused by lewisite showed that blisters may form because of the inhibition of cutaneous enzyme systems. Theories based on the suggestion that either inhibition of an epithelial enzyme or the action of an enzyme can cause blistering, and thus be responsible for the lesions of pemphigus, are at present of considerable interest.

Stoughton (1952) succeeded in isolating from the fæces of patients with ulcerative colitis an enzyme which had two different factors. Rothman (1954) referred to these as factors A and B. When incubated with formalin-fixed sections of human cells factor A destroyed the fibrils which joined the prickle-cells, and this was followed by the formation of intra-epidermal blisters. In other words the changes were very similar to those seen in pemphigus vulgaris. Thence arose the postulate that pemphigus is due to an enzyme which selectively attacks the tenofibrillary structures of the epidermis (in plain language the prickles or intercellular connections of the prickle-cell layer).

More recently Stoughton and Bagatell (1959) have shown that

cantharadin powder applied to fresh human skin in vitro will provoke acantholysis and blistering by releasing an enzymatic acantholytic factor or factors in the skin itself. It seems therefore that we are back where we started, and that pemphigus is due to a factor " X " which liberates enzymatic agents in the skin. Possibly as Scott (1958) has shown, endopeptidases may play a part in dissolving ground substance, and thus facilitate blister formation; in-vivo corticosteroids are used to control pemphigus, and in-vitro hydrocortisone inhibits the action of chymotripsin (which is an endopeptidase) possibly by decreasing the permeability of ground substance.

Aphthosis

Finally I want to put before you the views expressed by Touraine (1955) concerning " L'aphtose ", which I translate as aphthosis. To approach this subject somewhat obliquely; Hulusi Behçet (1889-1948) was appointed professor of dermatology in the University of Istanbul in 1933. In each of the years 1937 to 1940 he published accounts of a rare malady characterised by relapsing iritis and recurrent ulceration in the mouth and on the genitalia.

These lesions constitute a primary triad of symptoms. Curth (1946) and Phillips and Scott (1955) have suggested that the diagnosis should be made when two of these main features are present, for, as Carr (1957) has shown, oral and genital ulceration may precede the ocular symptoms by many years.

In nearly all cases associated complaints may be of greater immediate concern to the patients: these include skin lesions resembling erythema nodosum, erythema multiforme, arthralgia, non-articular arthritis, various signs of involvement of the central nervous system (the neuropathology has been well described by McMenemey and Lawrence [1957], thrombophlebitis, and occasionally cellulitis. Elsewhere I have summarised the recent work on this disease (MacKenna 1958).

Suffice it to say that the most usual manifestations of Behçet's malady, although often painful, are relatively benign. The long-term effects on vision may be disastrous but the patient's life is not in danger except when the central nervous system is involved; death then ensues in 50% of the cases (Evans et al. 1957).

Sezer (1953) was the first to claim isolation of a causal virus, and Evans et al. (1957) have confirmed Sezer's finding. McMenemey and Lawrence consider that both the neurological episodes and the fluctuations in the malady as seen elsewhere could be explained on the basis of recurrent viræmic phases. In this malady ulcers of the mouth are usually multiple and may begin as superficial erosions or as indurated nodules (Carr 1957). The bases of the erosions may be clean or covered with yellow slough. Fully developed, they may be 1–2 cm. in diameter, with shelving edges and without induration. The oral lesions cause pain on mastication and heal in about 2 weeks, but usually recur.

Touraine (1955) implied that the late Professor Behçet was fortunate in having his name applied to the syndrome, as aphthous ulceration of the mouth and genitals was described by several earlier authors, starting with Isnard (1818): he gives Neumann (1895) the credit for the term " aphthosis ".

Touraine's view, as I understand it, is that all forms of aphthous ulceration, from the simplest to periadenitis mucosæ necrotica recurrens (Sutton 1911) and Behçet's malady, are variants of the same disorder. If he is correct in this, the virus must be present in a large sample of the population. On a theory of lowered resistance in a few people we could explain *la grande aphtose* (which we call Behçet's malady), and also the fact that, although the patient harbours a virus, cross-infection of relations, nurses, and doctors seems not to be recorded. According to Touraine aphthous ulceration has been described in the nasal mucosa, the pharynx, and the œsophagus. Further, whilst skin-puncture sensitivity † in Behçet's disease was recorded by France et al. (1951), aphthosis can occasionally involve the skin alone, the signs being a recurrent necrotic pseudofolliculitis. In many cases of apparently simple aphthous ulceration concomitant ulceration occurs on the genitals, but the patient does not mention it, and we do not inquire.

If Touraine's views are correct, aphthosis would seem to be an interesting field for immunologists. Like herpes, it is a virus disease attacking both skin and mucosa; but, unlike the virus of herpes zoster, aphthosis virus has no special affinity for nerve-tissue. At present the chief interest of this subject is whether or not one should accept Touraine's view of the relation between most forms of aphthous ulceration; and Ito (1959) in Japan seems to be reaching conclusions which correlate with those of Touraine.

I should like gratefully to acknowledge the debt I owe to Dr. E. Lipman Cohen, who has generously helped me in the search for references; to Dr. Peter Borrie for constructive criticism; and to Dr. Aileen Scott for suggestions and assistance.

REFERENCES

Behçet, H. (1937) *Derm. Wschr.* **105**, 1152.
Bloch, B. (1927) *Arch. Derm. Syph., Berlin*, **153**, 20.
Borrie, P. (1958) *in* Roxburgh's Diseases of the Skin. London.
Brünauer, S. R. (1925) *Acta derm.-venereol., Stockh.* **6**, 131.
Burnet, M. (1959) *Brit. med. J.* ii, 645.
Carr, G. R. (1957) *Lancet*, ii, 358.
Church, R. E., Sneddon, I. B. (1953) *Brit. J. Derm.* **65**, 235.
Civatte, A. (1943) *Ann. Derm. Syph., Paris*, **3**, 1.
Cohen, H. R., Ullman, T. D., Dostrovsky, A. (1958) *J. invest. Derm.* **30**, 207.
Cooke, B. E. D. (1954) *Brit. dent. J.* **96**, 1.
Costello, M. J., Jaimovich, L., Dannenberg, M. (1957) *J. Amer. med. Ass.* **165**, 1249.
Curth, H. O. (1946) *Arch. Derm. Syph., Chicago*, **54**, 179.
— (1955) *Brit. J. Derm.* **67**, 324.
Darling, A. I., Crabb, H. S. M. (1955) *Oral Surg.* **8**, 47.
Derksen, J. C., Heringa, G. C., Weidinger, A. (1937) *Acta neerl. morph.* **1**, 31.
Director, W. (1952) *Arch. Derm.* **66**, 343.
Evans, A. D., Pallis, C. A., Spillane, J. D. (1957) *Lancet*, ii, 349.
Foot, N. C. (1947) *Amer. J. Path.* **23**, 1.
France, R., Buchanan, R. N., Wilson, M. W., Sheldon, M. B., Jr. (1951) *Medicine, Baltimore*, **30**, 335.
Freudenthal, W. (1926) *Arch. Derm. Syph., Berlin*, **152**, 505.
Gibb, A. G. (1958) *J. Laryng.* **72**, 799.
Goldsmith, W. N. (1936) Recent Advances in Dermatology. London.
Grace, A. W., Schwartz, H. J. (1934) *Arch. Derm. Syph., Chicago*, **29**, 651.
Hall, W. H., Finegold, J. (1953) *Ann. intern. Med.* **38**, 533.
Isnard (1818) cited by Touraine, A. (1941).
Ito, K. (1959) *Bull. pharm. res. Inst. (Osaka-Takaturi, Nippon)*, no. 21, p. 19; no. 22, p. 1.
Lever, W. F. (1953) *Medicine, Baltimore*, **32**, 1.
Lewis, T. (1927) The Blood-vessels of the Human Skin and Their Responses. London.
MacKenna, R. M. B. (1958) *in* The Medical Annual (edited by H. Tidy and R. Milnes Walker). Bristol.
MacLeod, J. M. H. (1903) Practical Handbook of the Pathology of the Skin. London.
McMenemey, W. H., Lawrence, B. J. (1957) *Lancet*, ii, 353.
Mali, J. W. H. (1956) *J. invest. Derm.* **27**, 451.
Neumann, I. (1895) cited by Touraine, A. (1941).
Norrino, A., Yaffee, H. (1957) *Arch. Derm.* **76**, 357.
Peters, R. A., Sinclair, H. M., Thompson, R. H. S. (1946) *Biochem. J.* **40**, 516.
Pinkus, H. (1939) *J. Invest. Derm.* **2**, 175.
— (1958) *Dermatologica, Basel*, **117**, 369.
— (1959) *J. invest. Derm.* **33**, 171.
Roe, D. A. (1959) *Arch. Derm.* **80**, 210.
Rooke, A., Waddington, E. (1953) *Brit. J. Derm.* **65**, 425.
Rothman, S. (1954) Physiology and Biochemistry of the Skin. Chicago.
Scott, A. (1958) *J. invest. Derm.* **30**, 201.
Sezer, F. N. (1953) *Amer. J. Ophthal.* **36**, 301.
Shellow, H. (1958) *Amer. J. med. Sci.* **235**, 456.
Stoughton, R. B. (1952) *Science*, **116**, 37.
— Bagatell, F. (1959) *J. invest. Derm.* **33**, 287.
Sutton, R. L. (1911) *J. cutan. Dis.* **29**, 65.
Sutton, R. L., Jr. (1956) Diseases of the Skin. St. Louis.
Taylor, M. (1958) *J. Laryng.* **72**, 365.
Touraine, A. (1941) *Bull. Soc. franç. Derm. Syph.* **48**, 61.
— (1955) *Pr. méd.* **63**, 1493.
Thomson, M. S. (1928) *Brit. J. Derm.* **40**, 191.
Tzanck, A., Melki, G. R. (1954) Modern Trends in Dermatology (edited by R. M. B. MacKenna). London.
Usher, B. (1933) *Arch. Derm. Syph., Chicago*, **28**, 488.
Warin, R. P., Crabb, H. S. M., Darling, A. I. (1958) *Brit. med. J.* i, 983.
Watkyn-Thomas, F. W. (1955) *in* The Medical Annual (edited by H. Tidy and R. Milnes Walker). Bristol.
Yoffey, J. M. (1958) *J. Laryng.* **72**, 377.

† Skin-puncture sensitivity: a prick with a sterile needle is followed by the appearance of a painful red nodule or pustule.

CORTICOSTEROIDS IN PREOPERATIVE MEDICAL MANAGEMENT OF ULCERATIVE COLITIS

DO THEY AFFECT SURGICAL SUCCESS?

W. B. EWART
B.Sc., M.D. Manitoba
CLINICAL ASSISTANT, ST. MARK'S HOSPITAL, LONDON, E.C.1

J. E. LENNARD-JONES
M.B. Cantab., M.R.C.P.
MEMBER OF MEDICAL RESEARCH COUNCIL DEPARTMENT OF CLINICAL RESEARCH, UNIVERSITY COLLEGE HOSPITAL; RESEARCH FELLOW, ST. MARK'S HOSPITAL

From the Research Department, St. Mark's Hospital

CORTICOSTEROIDS are of proved value in the medical treatment of ulcerative colitis (Truelove and Witts 1955, 1959); but a current surgical view is expressed by Goligher (1959): "Physicians should remember the troubles they are creating for the surgeon when they embark on cortisone therapy." It is not feasible to investigate by a controlled trial whether corticosteroids make operation more hazardous because these drugs cannot now be withheld if they are indicated. We have therefore made a retrospective study of the effect of corticosteroids on surgical treatment at St. Mark's Hospital, London, where many patients with ulcerative colitis are treated by a small surgical staff using a standard technique. Most patients in this series were treated medically with corticosteroid drugs at other hospitals, and therefore the conditions under which these drugs were used cannot be defined.

Method of Study

Between the end of 1951 and July, 1959, the operation most commonly performed at St. Mark's Hospital for the treatment of ulcerative colitis was one-stage subtotal colectomy and ileostomy; 131 patients were treated in this way. So as to simplify our investigation we have studied the results of this operation alone; and we have not studied the results of rectal excision at a second stage, subtotal colectomy after preliminary ileostomy, subtotal colectomy with ileorectal anastomosis, or one-stage procto-colectomy. We have compared the post-operative course after one-stage subtotal colectomy and ileostomy in patients who had received corticosteroids with those who had not; and we have further studied the steroid group to see whether surgical results were affected by the duration or dose of steroids given.

A patient was placed in the "*steroid group*" if he had been given corticosteroid drugs at any time during the year before operation.

Most patients received cortisone, at least 200 mg. daily, equivalent doses of other corticosteroids, or corticotrophin at least 60 units daily, for a week or longer and then smaller doses. A few patients received these large initial doses more than a year before operation, followed by a maintenance dose equivalent to cortisone 75 mg. daily. 2 patients received hydrocortisone hemisuccinate, 100 mg. daily by retention enema, for ten days as the only corticosteroid treatment The term "*cortisone cover*" for an operation indicates that cortisone, 500 mg., was given over four days beginning two days preoperatively.

TABLE I—SURGICAL RESULTS IN PATIENTS UNTREATED WITH CORTICOSTEROID DRUGS AND IN PATIENTS TREATED WITH THESE DRUGS (GROUPS A AND B CONTAIN PATIENTS WHO WERE MILDLY ILL BEFORE OPERATION, GROUPS C AND D THOSE WHO WERE SEVERELY ILL).

—	Medical treatment	Group A	Group B	Group C	Group D	Total
No. of cases	Non-steroid	21 (26%)	30 (38%)	20 (25%)	8 (10%)	79
	Steroid	8 (15%)	14 (26%)	20 (39%)	10 (20%)	52
Deaths	Non-steroid	0	0	2	3	5
	Steroid	1	0	2	4	7
Complicated recovery	Non-steroid	7	6	8	4	25
	Steroid	2	3	8	2	15

We have divided the patients into four groups according to their preoperative clinical condition and without any reference to their subsequent progress or the pathological appearance of the bowel excised.* The number of patients in each group is shown in table I.

Group A (Good general condition; inactive colitis).—Patients with chronic colitis of more than two years' duration, without recent weight loss, fever, or tachycardia. Operation undertaken because of chronic disablement, local complications, or the possibility of cancer.

Group B (Good general condition; mild active colitis).—Patients with active colitis who were not emaciated or dehydrated, whose temperature did not persistently exceed 100°F or pulse-rate exceed 100 per minute, and without abdominal distension. Operation undertaken during an active phase of the disease but for the same reasons as in group A.

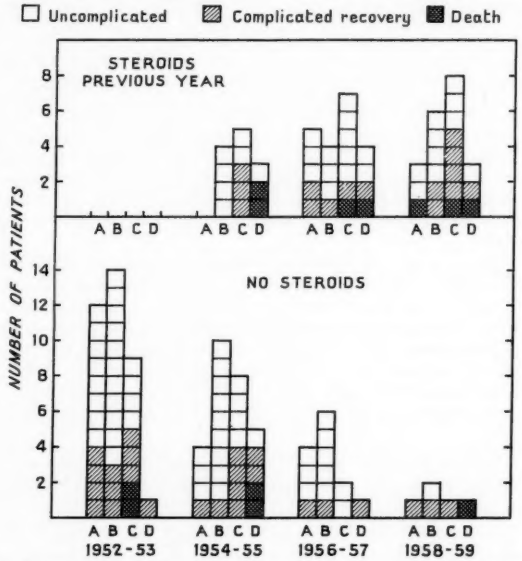


Fig. 1—Number of patients in groups A to D (increasing severity of illness) and number who had received corticosteroids during different periods of this study.

Group C (poor general condition and/or severe active colitis).—Patients who were emaciated, or severely depleted of fluid and electrolytes; or with fever persistently over 100°F, sustained pulse-rate above 100 per minute, or abdominal distension. Operation considered essential, but elective, because of the failure of medical treatment to induce remission.

Group D (Emergency operations for critically ill patients).—Patients with fulminating disease, rapidly deteriorating chronic disease, or acute complications such as perforation of the bowel.

COMPARABILITY OF THE "STEROID" AND "NON-STEROID" GROUPS

The steroid group contains a higher proportion (59%) of patients in groups C and D (table I) who were severely ill at the time of operation than the non-steroid group (35%). This difference between the two groups can be partly overcome by

* We are very grateful to Mr. W. Southwood, F.R.C.S., for independently repeating this division so as to give some estimate of the error involved. He grouped 17 patients (13%) differently:
Group A: 8 out of 29 re-classed B.
Group B: 8 out of 44 re-classed C.
Group D: 1 out of 18 re-classed C.
Our general conclusions are unchanged if the patients are regrouped in this way.

examining groups A to D separately; in Groups C and D there are approximately equal numbers from the steroid and non-steroid groups, allowing a convenient direct comparison. In other respects, the steroid and non-steroid groups appear comparable:

Age of the patients.—The mean age of the 79 patients in the non-steroid group was 41 years (S.D. 13) and of the 52 patients in the steroid group 37 years (S.D. 13)

Patients with associated diseases.—Only 2 patients had diseases other than colitis likely to make operation hazardous: both had received corticosteroids. One, with chronic pyelonephritis, died from infective enteritis; the other, who had had a stroke, recovered uneventfully.

Factors depending on the year of operation (fig. 1).—In 1952–53 there was a higher proportion of patients in groups A and B than in later years. In 1954 the 1st patient who had received corticosteroids was operated on, and the proportion of these patients has steadily increased to become the majority. If groups A–D are examined separately the results of treatment during the years of this study have remained constant: this is true in both the non-steroid and steroid groups. Analyses of short periods—e.g. 1954–57—or even one year such as 1956, when the numbers in the steroid and non-steroid groups were similar, yield the same pattern of results as overall comparisons.

Results

COMPARISONS BETWEEN STEROID AND NON-STEROID GROUPS

Mortality (tables I and II)

There were 7 deaths (13%) in the steroid group and 5 (6%) in the non-steroid group. Among the patients severely ill at the time of operation (groups C and D) the mortality was equal: 11 of the 12 deaths occurred among these patients.

Peritonitis caused more than half the deaths in both groups; the other principal cause of death in both groups was immediate postoperative circulatory collapse unresponsive to hydrocortisone and other treatments.

Morbidity (tables I and III, fig. 2)

A complicated recovery (defined as the occurrence of any complication, even a stitch abscess) occurred with equal frequency in the two groups. Table III suggests that individual complications were commoner in the steroid group. As a measure of the severity of complications we have examined the number of days elapsing between operation and discharge from hospital. The average time

TABLE II—CLINICAL DETAILS OF FATAL CASES

Case no.	Age (yr.)	Sex	Corticosteroid		Preoperative Group	Operation	Postoperative course	Day of death	Necropsy	Comment
			Treatment	Cover						
44	35	M	Nil	..	D: emaciated, œdema, arthritis; deteriorating rapidly	Bowel adherent and œdematous; free fluid; operative tear	Circulatory collapse on 4th day	4	General peritonitis	General peritonitis causing circulatory collapse and death
22	26	M	Nil	..	C: active disease with severe bleeding	Bowel distended with 2 perforations localised as abscesses	Pyrexia 5th day; circulatory collapse 7th day	7	General peritonitis	General peritonitis causing circulatory collapse and death
52	67	F	Nil	..	D: stuporous, high fever, abdominal distension	Sealed preoperative perforation of cæcum	Rigor 5th day followed by circulatory collapse	6	Peritonitis	General peritonitis causing circulatory collapse and death
72	33	M	Nil	..	D: mental confusion high fever, abdominal distension	Distended cæcum and ileum, ascites; operative tear of splenic flexure	Immediate circulatory collapse	1	No local cause of death	Circulatory collapse. ? Cause
8	56	F	Nil	..	C: thin; active colitis for 6 weeks	Uneventful	Uneventful, but sudden death when ready for discharge	21	No cause of death found	Unexplained sudden death
74	19	M	Cortisone, 200 mg. daily for 21 days	0	D: very poor; abdominal distension, rebound tenderness	Preoperative perforation of cæcum with general peritonitis	Improved for 19 days, then pulmonary infarct and septicæmia	25	Pelvic abscess, pulmonary infarct, septicæmia	Preoperative perforation causing peritonitis and septicæmia
93	48	F	Corticotrophin 6–2 weeks preoperatively	+	C: deteriorating, chronic disease	Operative tear of splenic flexure	Circulatory collapse 3rd day; continued shock, electrolyte imbalance, severe wound infection	19	None	Probable peritonitis and severe wound infection following operative tear of grossly diseased bowel
115	28	M	Prednisone 30 mg. daily for 10 weeks	+ 0	D: Critically ill, fever 102–103°F; deteriorating	Adherent colon; uneventful	Pyrexia, ileus, electrolyte imbalance; circulatory collapse after second laparotomy for drainage of abscess	20	Multiple intra-abdominal abscesses, septicæmia	Peritonitis without bowel perforation; no steroid cover for second laparotomy
58	33	F	Cortisone 200 mg. daily from 13th to 5th preoperative day	0	D: emaciated and weak, purpura; steady deterioration	Bowel adherent; two operative tears, gross contamination	Immediate circulatory collapse	5	? Peritonitis	Death probably due to peritonitis and possibly adrenal failure
111	58	M	Continuous steroids for 4 years; prednisone 40 mg. daily	+	C: very ill; severe diarrhœa after oxytetracycline, chronic pyelonephritis	Uneventful	Well 10 days; then bloody ileostomy discharge, jaundice, and collapse	16	Infective hæmorrhagic enteritis	Enteritis following oxytetracycline
126	44	M	8 weeks of corticotrophin ended 8 weeks before operation	+	D: profuse diarrhœa, gross hypoproteinæmic œdema	Colon distended and œdematous; uneventful	Immediate circulatory collapse	2	No local cause of death	Postoperative circulatory collapse. ? Cause
131	51	M	Continuous steroids for 4 years; prednisone 15 mg. daily	+	A: long history of relapsing colitis, but in remission; condition good	Uneventful	Circulatory collapse 24 hours after operation	2	None	Postoperative circulatory collapse. ? Cause

was 34 days in the steroid group and 28 days in the non-steroid group—a significant difference ($P=0.02$). It seems likely (fig. 2) that part of this difference can be ascribed to the different proportion of "good risk" (groups A and B) and "poor risk" (groups C and D) patients in the two groups, but the numbers are too few to be conclusive.

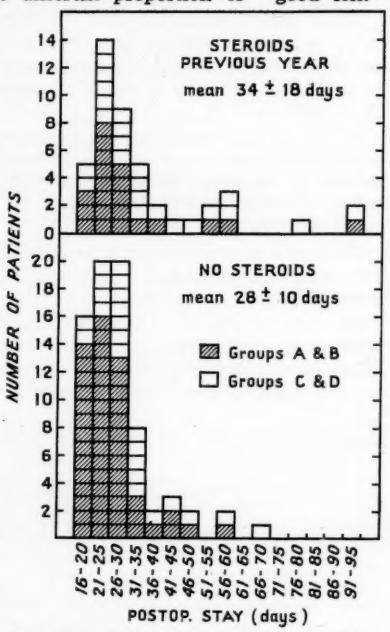


Fig. 2—Length of stay in hospital after operation.

Friability of Bowel, Perforation, and Peritonitis (table IV)

Preoperative perforation of the bowel occurred with equal frequency in the steroid and non-steroid groups. Surgical perforation of the bowel was more frequent in the steroid group (6 cases) than in the non-steroid group (3 cases); 1 patient who had not received any steroid drugs during the previous six months is included in the steroid group. The consequences of bowel perforation were equally dire in the two groups.

6 out of the 7 preoperative perforations had become sealed to neighbouring structures without peritonitis or were surrounded by a localised abscess at the time of operation. In 4 patients peritonitis spread when adhesions around a perforation or abscess had to be broken down during mobilisation of the bowel. No spread occurred in 2 others, probably because the perforation had occurred in the pelvic colon and could be left undisturbed during subtotal colectomy. Perhaps the finding of a sealed perforation or localised abscess around the colon is one indication for preliminary ileostomy, with colectomy later.

Perforation of the bowel at operation is apparently associated with the severity of the illness, because all the patients except 1 were in Groups C or D. Peritonitis followed perforation before or at operation in 10 patients, and 6 patients escaped it. Peritonitis without apparent perforation of the bowel developed in only 1 patient.

TABLE III—INDIVIDUAL POSTOPERATIVE COMPLICATIONS (SEVERAL COMPLICATIONS MAY HAVE OCCURRED IN THE SAME PATIENT)

Complication	Steroid (52 patients)	Non-steroid (79 patients)
Technical *	6	14
Circulatory:		
Collapse	8	8
Thrombotic	3	4
Infection:		
Intra-abdominal	7	6
Burst abdomen	2	2
Major wound	0	1
Minor wound	9	7
Respiratory	2	5
Miscellaneous	4	2
Other		
Jaundice	2	1
Gastrointestinal hæmorrhage	0	1

* Intestinal obstruction and ileus treated conservatively 8.
" " " requiring laparotomy 9.
Miscellaneous 3." " "

A careful pathological examination has been made of every colon removed in this series, and we have not been able to find any difference between the colons removed from those who had been given steroid drugs and those who had not. In 5 cases the surgeon or pathologist remarked on the friability of the bowel wall, and twice it was said to "tear like blotting-paper"; only 1 of these 5 patients had received steroids.

Circulatory Collapse

This occurred in 8 cases in both the steroid and the non-steroid groups; 4 patients in each group died from this cause. In all but 2 cases, one of whom had been given corticosteroids (including the usual operative cover) and the other not, collapse could be attributed to peritonitis or dehydration.

The death of these 2 patients who died in shock, unresponsive to hydrocortisone, a few hours after operation, is unexplained. General peritonitis presented as circulatory collapse without other signs in 3 patients who had not received corticosteroids.

Among those who had received corticosteroids, shock occurred in 5 of the 38 patients given extra cortisone at the time of operation, and in 3 of the 15 not given cortisone cover. Lack of cortisone may have contributed to the collapse in these last 3 patients, but in every case it could readily be explained on other grounds.

DOES MANAGEMENT OF CORTICOSTEROID THERAPY INFLUENCE SURGICAL RESULTS?

Clinical Deterioration During Corticosteroid Therapy

Of the 31 patients who were treated with corticosteroids up to the time of operation, 15 became worse, the condition of 9 remained the same, and 7 improved a little. There was a dangerous delay in undertaking surgery for 3 of those who became worse; 2 of them died (cases 74 and 115, table II) and the recovery of the 3rd was delayed by sepsis. Probably undue reliance on corticosteroids, leading to lack of urgency, caused more harm to these 3 patients than the drugs themselves. The downhill course in the other 12 who became worse was not obviously altered by a trial of corticosteroid drugs, which caused no apparent harm.

TABLE IV—BOWEL PERFORATION AND RELATED COMPLICATIONS

—	Total	Postoperative course: Local peritonitis	General peritonitis	Circulatory collapse	Burst abdomen	Other wound infections	Deaths
Preoperative perforation:							
Non-steroid	4	2	1	1	2	0	2
Steroid	3	3	0	0	0	1	1
Perforation during operation:							
Non-steroid	3	0	1	2	0	0	2
Steroid *	6	2	1	4	2	3	2

* In 1 of these cases no corticosteroid drugs had been administered preoperatively and none was given at the time of operation.

Surgical Results after Large Doses of Corticosteroids

We can find no correlation between the preoperative dose of corticosteroids and surgical result.

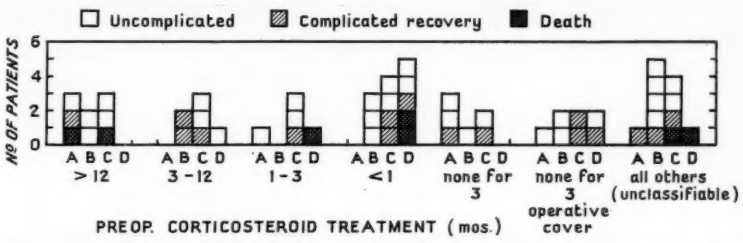


Fig. 3—The results of operation in patients treated continuously with corticosteroids for different times.

Of the 13 patients who received at least 200 mg. of cortisone or 80 units of corticotrophin daily (excluding cover) during the three days before operation, 2 died and 2 made a complicated recovery. These results are similar to those in the 18 cases in which lower doses were given during these three days; of these 18 patients, 3 died and 6 made a complicated recovery.

Of the 16 patients who died or were detained in hospital for more than forty days after operation (using this criterion as an arbitrary definition of a seriously complicated recovery), 10 were receiving the drugs up to the time of operation and 6 were not. The duration of treatment among the former ranged from four days to four years; 6 were receiving less than cortisone 200 mg. daily or corticotrophin 80 units daily, and 4 patients these or greater doses.

Surgical Results after Lengthy Corticosteroid Therapy

Fig. 3 shows no obvious relation between the length of continuous treatment with corticosteroids before operation and the postoperative result. Perhaps fortuitously, the only 2 patients who were treated continuously for as long as four years both died (cases 111 and 131).

Discussion

There is much experimental and clinical evidence that corticosteroids lower resistance to infection (Thomas 1955, Slaney and Brooke 1958), predispose to circulatory collapse (Bayliss 1958) and possibly to venous thrombosis (Thorn et al. 1954, p. 91), and impair wound healing under certain conditions (Thorn et al. 1954, pp. 88, 106). It is, therefore, perhaps surprising that we have demonstrated only small differences in the surgical results between patients treated with corticosteroid drugs and those not treated in this way—particularly since many of the patients were emaciated, the operation often involved handling an acutely inflamed colon, and the doses of corticosteroids were often large. Among those treated with these drugs there was a slightly greater mortality and morbidity, longer stay in hospital after operation, and increased risk of perforation of the bowel at operation. Many of these differences were small, and a larger series would be needed to establish their significance. Some of the differences can be ascribed to a higher proportion of mild chronic cases in the non-steroid group and to occasional undue reliance on corticosteroid drugs during the exploratory years after their introduction.

Brooke (1956) described disintegration of the bowel wall as a complication of long-continued steroid therapy, but Goligher (1959) stated that he had encountered similar cases in which these drugs had never been administered. Clearly the results of corticosteroid treatment can be assessed only by comparison with a control series not given this treatment. Patients with ulcerative colitis who need surgery often have severe complications of the disease whatever treatment they have been given.

Our findings are very similar to those of MacDougall (1959), who has reported the results of surgical treatment since the introduction of corticosteroids in 130 patients, of whom about half had received these drugs and the other half, treated concurrently, had not. As in the present series, all patients were operated on by a small surgical staff at one hospital. Operative difficulties occurred with the same frequency in the two groups and surgical results were the same in the two groups. MacDougall took no account of the preoperative condition of the patients or the dose and duration of corticosteroid treatment. We know of no other series with which our findings can be compared. Hayes and Kushlan (1956) described a small series of 13 patients treated surgically, 7 after corticosteroid therapy and 6 untreated with steroids; 1 patient died in each group. Details of preoperative condition and postoperative complications are not given. During the Medical Research Council's therapeutic trial of cortisone (Truelove and Witts 1955) 9 patients treated with cortisone required surgical treatment and 2 died, whereas of 15 patients treated with inert tablets who needed operation 6 died. Popert and Davis (1958) reported an uncontrolled series which strongly suggests that corticosteroids do not greatly influence surgical results.

In this study we pay much attention to the high proportion of patients among those treated with corticosteroids who were severely ill at the time of operation. Two factors contribute to this. Firstly, fewer severely ill patients were treated by combined subtotal colectomy and ileostomy when the procedure was introduced at this hospital than in later years. Secondly, it has been shown (Truelove and Witts 1955) that cortisone induces remission more commonly in mild cases of colitis than in severe cases. These drugs are therefore likely to cause a disproportionate reduction in the number of mild cases submitted to operation and leave an apparent excess of severe cases in a surgical series composed largely of those for whom medical treatment has failed. Our results suggest that the poor condition of very few patients —probably only 3—can be attributed to the therapy. In each of these cases surgery was delayed too long despite serious clinical deterioration. Similar delay, with a fatal result (cases 44 and 72, table II), occurred twice among patients not receiving corticosteroids.

So far we have been concerned with possible adverse effects of corticosteroids. Have they a positive contribution to make towards surgical safety? We have shown that the mortality among patients in good general condition with inactive or mild colitis (groups A and B) was 1%, whereas the mortality among severely ill patients (groups C and D) was 19%. Improvement in surgical results seems likely, not so much from improvements in technique, as from a reduction in the number of patients who need operation at a time when they are severely ill. Corticosteroids induce remission in a high proportion of patients with colitis to whom they are given (Truelove and Witts 1955, 1959, Kirsner et al. 1959). We agree with Kirsner and his colleagues that appreciable benefit to the patient is often evident within two or three

days, and with MacDougall (1959) that most patients who are going to be helped by corticosteroids show definite improvement within the first eight days of treatment. If this early improvement is seen it is justifiable to continue treatment with these drugs until the greatest possible improvement is attained. If, however, there is no improvement but continued deterioration, persistence with this treatment, as with any other ineffective treatment, courts disaster (Brooke 1956, Goligher 1959).

We believe that no patient seriously ill with colitis should be operated on, except for acute complications, unless vigorous medical treatment aimed at improving his condition as much as possible has been applied. Corticosteroids in full doses should usually be given a short therapeutic trial as part of this regime. If all medical measures have failed, surgery should be undertaken quickly before deterioration in the patient's condition further prejudices the issue; if improvement in his condition can be won by medical measures, surgery becomes safer.

Conclusions

In this series of 131 patients with ulcerative colitis treated by one-stage subtotal colectomy and ileostomy, the mortality-rate was 9% and the complicated-recovery rate was 31%. The results of subsequent rectal excision have not been analysed.

There was slightly greater mortality, morbidity, length of stay in hospital after operation, and risk of surgical perforation of the bowel in the steroid group. The differences were small and can be partly ascribed to the fact that this group included fewer mild chronic cases of colitis than the group untreated with corticosteroids.

There was no correlation between the dose or duration of preoperative corticosteroid therapy and surgical result. Occasional bad surgical results followed undue persistence with medical treatment, with or without corticosteroids, until operation on a desperately ill patient offered the only chance of survival.

The mortality among 73 less ill patients was only 1%, whereas among the 18 most severely ill patients it was 40%. Vigorous medical treatment, including corticosteroids when indicated, can contribute to surgical safety by reducing the proportion of patients who have to be operated on when they are very ill.

We are grateful to the consultant staff of St. Mark's Hospital for permission to study their records and publish these results. The secretarial expenses of this investigation were defrayed out of a block grant to the research department of St. Mark's Hospital from the board of governors of the Hammersmith and St. Mark's group of hospitals.

REFERENCES

Bayliss, R. I. S. (1958) *Brit. med. J.* ii, 935.
Brooke, B. N. (1956) *Lancet*, ii, 1175.
Goligher, J. C. (1959) *Scot. med. J.* **4**, 1.
Hayes, M. A., Kushlan, S. D. (1956) *Gastroenterology*, **30**, 75.
Kirsner, J. B., Palmer, W. L., Spencer, Jean A., Bicks, R. O., Johnson, C. F. (1959) *Ann. Intern. Med.* **50**, 891.
MacDougall, I. P. M. (1959) *Proc. R. Soc. Med.* **52**, suppl. (Anglo-American Conference on Proctology); p. 9.
Popert, A. J., Davis, P. S. (1958) *Lancet*, i, 21.
Slaney, G., Brooke, B. N. (1958) *ibid.* i, 504.
Thomas, L. (1955) *Bull. N.Y. Acad. Med.* **31**, 485.
Thorn, G. W., Jenkins, D., Laidlaw, J. C., Goetz, F. C., Dingman, J. F., Arons, W. L., Streeten, D. H. P., McCracken, B. H. (1954) *in* Medical Uses of Cortisone (edited by F. D. W. Lukens); chap. 2. New York.
Truelove, S. C., Witts, L. J. (1955) *Brit. med. J.* ii, 1041.
— — (1959) *ibid.* i, 387.

BLOOD-GROUPS AND SECRETOR STATUS IN ULCERATIVE COLITIS

N. E. WINSTONE
M.B. Lond., F.R.C.S.
TEMPORARY LECTURER IN SURGERY, UNIVERSITY OF BIRMINGHAM

A. J. HENDERSON
SENIOR TECHNICIAN, BLOOD-TRANSFUSION LABORATORY, QUEEN ELIZABETH HOSPITAL, BIRMINGHAM

B. N. BROOKE
M.D. Birm., M.Chir. Cantab., F.R.C.S.
READER IN SURGERY, UNIVERSITY OF BIRMINGHAM

DURING the past decade the association of certain diseases with particular blood-groups has been demonstrated. Thus duodenal ulcer has an association with group O, while in cases of gastric ulcer this group is in only slight preponderance (Race and Sanger 1958). Carcinoma of the stomach, addisonian anæmia, and salivary-gland tumours tend to arise more commonly in group-A patients (Aird et al. 1953, *British Medical Journal* 1956, Cameron 1958). Duodenal ulcer is relatively commoner in non-secretors of group-specific substances than in secretors (Clarke et al. 1956).

We describe here a survey of another condition of non-specific ulceration of unknown ætiology in the alimentary tract—namely, ulcerative colitis.

Methods

277 cases of ulcerative colitis were grouped into their ABO and rhesus categories by the usual methods (Medical Research Council 1943, 1952). In 261 the diagnosis was proven at operation when the diseased bowel was removed; in the 16 cases not operated on, the diagnosis was determined by the presence of chronic non-specific bloody diarrhœa with characteristic radiological changes at barium enema. Any case with steatorrhœa or small-bowel changes was excluded on the grounds that enterocolitis or Crohn's disease of the small and large intestine may constitute other disease entities (Brooke 1959).

163 of these cases also had their secretor status investigated, by the method of McConnell (Clarke et al. 1956), the anti-H substance being obtained from the seeds of *Ulex europæus*. Originally all specimens of saliva were tested with both ulex extract and anti-A and/or anti-B sera; there was complete correlation. Therefore in the later specimens only the non-secretors of groups A_1, A_1B, or B were also tested against the anti-A and/or anti-B sera. Control figures for the ABO and rhesus distribution in the five counties of the Midlands were obtained from the records of the Royal Institute of Anthropology. No figures are available for the normal distribution for secretors in this area; those for 491 normal people in the Liverpool region were, therefore, taken as an indication of the control secretor distribution (Clarke et al. 1956).

Results

The results are shown in tables I and II.

TABLE I

Group	Ulcerative colitis		Controls *
	No.	%	
ABO:			
O	132	47·7	46·01
A	117	42·2	42·78
B	21	7·6	8·10
AB	7	2·5	3·11
Total	277	..	..
Rhesus-negative ..	47	17·0	17·85

* From 39,084 blood donors in the West Midlands.

$\chi^2 = 0{\cdot}18$. $P < 0{\cdot}7$.

Standard deviation for group O $= \sqrt{\frac{46 \times 54}{277}} \simeq 3$.

For results to be significant at 5% level group O would have to lie outside the range $46 \pm 6\%$.

TABLE II

Secretor status	Ulcerative colitis		Controls *
	No.	%	
Secretors	117	71·1	75·8
Non-secretors	46	28·9	24·2
Total	163	..	..

* From 491 healthy persons in Liverpool region.

$\chi^2 = 1{\cdot}43$. $0{\cdot}2 < P < 0{\cdot}3$.

Standard deviation $= \sqrt{\frac{24{\cdot}2 \times 75{\cdot}8}{163}} = 3{\cdot}35$

For results to be significant at 5% level, the non-secretors have to be outside the range $24{\cdot}2 \pm 6{\cdot}7\%$.

Discussion

In this somewhat limited series the ABO and rhesus distribution in ulcerative colitis very closely resembles the control figures. Thus it appears that ulcerative colitis has no predilection for those with any one of the ABO blood-groups, nor is this disorder correlated with the rhesus factor. Secretor distribution is also well within normal limits. It is not, however, possible to be certain that no such associations exist until further series have been studied.

Summary

The ABO blood-group and rhesus factor were determined in 277 cases of ulcerative colitis; 163 had their secretor status investigated. The results fall within the normal pattern of the control series.

We thank Dr. J. N. M. Chalmers, Dr. A. J. Tooth, Dr. J. A. H. Waterhouse, and Dr. W. Weiner for their help in this work.

REFERENCES

Aird, I., Bentall, H. H., Roberts, J. A. F. (1953) *Brit. med. J.* i, 799.
British Medical Journal (1956) ii, 723.
Brooke, B. N. (1959) *Lancet*, ii, 745.
Cameron, J. M. (1958) *ibid.* i, 239.
Clarke, C. A., Edwards, J. W., Haddock, D. R. W., Howell-Evans, A. W., McConnell, R. B., Sheppard, P. M. (1956) *Brit. med. J.* ii, 725.
Medical Research Council (1943) Memorandum no. 9. Determination of Blood Groups. H.M. Stationery Office.
— (1952) Memorandum no. 27. Rh Blood Groups and Their Clinical Effects. H.M. Stationery Office.
Race, R. R., Sanger, R. (1958) Blood Groups in Man; p. 322. Oxford.

THE TREATMENT OF PRIMARY RAYNAUD'S DISEASE OF THE UPPER LIMB

J. H. PEACOCK
M.Ch. Birm., F.R.C.S.
LECTURER IN SURGERY, UNIVERSITY OF BRISTOL

IT is now generally accepted that the vascular phenomena Raynaud described in 1862 are more accurately grouped into primary and secondary forms. Little advance, however, has been made in the treatment of the primary disease since the advent of sympathetic ganglionectomy which followed the work of Hunter and Royle in 1924.

Although lumbar sympathectomy is both the best immediate and the best long-term treatment for Raynaud's disease of the lower limb, in the upper limb sympathectomy has been found far less satisfactory, particularly when long-term results are compared with those obtained, within the first six months. Although in some cases considerable permanent benefit results from the operation, the exact degree seems to vary widely (Ross 1935, Simmons and Sheehan 1939, Smithwick and White 1946, Felder et al. 1949). This is due not only to differences in clinical classification and selection of cases but also to differences in the times at which operative results are assessed and reported. The initial improvement after sympathectomy depends on the amount of structural disease in the digital vessels, where sympathetic tone is high. Relapse later is always associated with a return of sympathetic nervous activity (Felder et al. 1949); and, although this seldom reaches the preoperative level, it usually causes continuing disability. In many such cases, although the intense pain and pallid phase of the attacks have been relieved, in varying degree, they are replaced by a cold cyanotic stage which may be long-continued and associated with considerable aching, joint stiffness, and œdema of the digits.

A satisfactory operation has yet to be devised which will ensure, in the majority of cases, complete long-term removal of sympathetic nervous control of the hand blood-vessels (Barcroft and Hamilton 1948, Robertson and Smithwick 1951). Moreover, in my experience, no long-term benefit has followed a second operation in cases in which sympathetic activity has returned. In 11 hands in which the initial operation had been excision of the 2nd and 3rd dorsal sympathetic ganglia, removal of scar tissue from the previous operative site, together with excision of the stellate ganglion, was followed by vasodilatation which lasted for only a few days or weeks, and in no case was sympathetic control of the hands found to be absent when tested six months later by indirect body heating (Landis and Gibbon 1933).

Vasodilator drugs, as a group, have also been disappointing, mainly because of the inherent difficulties of applying drugs with a generalised systemic action to ambulatory patients with a localised arterial abnormality. With short-acting compounds, the degree of sympathetic blockade is uncertain: at one time it may be clinically ineffective while at others there may be so large a hæmodynamic shift that in the erect position there is little if any increase in the hand blood-flow.

Some observations made by me in 1954–55 indicated not only that the peripheral venous concentrations of adrenaline and noradrenaline were increased in Raynaud's disease (Peacock 1959) but also that this abnormality was often linked with a relatively low level of basal heat production which was manifest clinically as cold sensitivity and shivering. The cause of this latter abnormality was not at that time apparent, but further investigations have shown that many of such patients are in a state of relative hypopituitarism in which the serum protein-bound iodine is low and the urinary excretion of 17-ketosteroids and œstrogens is diminished (Peacock, to be published).

In view of the work of Roth and Sheard (1950), who demonstrated that basal heat production regulates the ability of the peripheral circulation to undergo dilatation or withstand constriction by cold, experiments were undertaken to establish whether measures to correct the two abnormalities would be of value.

The drugs used were reserpine and triiodothyronine. Reserpine was chosen because at that time its effect was thought to be mainly on the hypothalmus, and studies suggested that, although it was less powerful than the shorter-acting adrenergic blocking agents, its level of sympathetic blockade was more stable and ambulatory patients could be controlled more easily with it than with other vasodilator drugs then available.

Triiodothyronine was used in order to see whether the patient's own heat-production could be increased to such an extent that peripheral vasodilation would be induced without toxic manifestation of overdosage. Triiodothyronine was considered preferable to thyroid, not only

* Part of a paper presented to the Surgical Research Society, May, 1958.

because previous workers had failed to produce improvement in Raynaud's disease with thyroid but also because reports were beginning to appear which suggested that cases of hypometabolism with cold sensitivity could be benefited by triiodothyronine when thyroid therapy had failed (Freedberg et al. 1955, Kurland et al. 1955, Tittle 1956).

Investigation

Initially two pilot studies were undertaken.

Pilot Study no. 1

Reserpine 0·25 mg. t.d.s. was given in 6 cases of primary Raynaud's disease for two weeks.

The digital temperatures were recorded from the pulp of the right index finger, in a temperature-controlled room at 20°±0·5°C, by a thermistor calibrated to 0·1°C accuracy. The hand blood-flows were estimated at the same room temperature with a thermostatically controlled water-filled venous-occlusion plethysmograph with the water temperature at 32°±0·5°C. The metabolic rates were measured under inpatient basal conditions by means of a Benedict-Roth spirometer, the mean of three consecutive readings being taken as the final value.

TABLE I—EFFECT OF RESERPINE 0·25 MG. T.D.S. FOR 14 DAYS ON THE RESTING TEMPERATURE OF THE RIGHT INDEX FINGER AND HAND BLOOD-FLOWS

Case	Previous sympathectomy	Nutritional lesions	Temperature of right index finger (°C)		Hand blood-flows (ml. per 100 ml. per min.)		Basal metabolic rate (%)
			Before	After	Before	After	
1	No	No	20·6	20·4	2·7	2·2	0
2	No	No	20·8	31·6	2·4	7·0	+15
3	No	No	20·2	23·8	3·2	2·9	0
4	No	No	20·0	33·4	1·7	6·8	+10
5	No	No	25·4	26·2	3·4	4·1	− 8
6	Yes	Yes	20·2	20·4	2·2	2·5	−14

Room temperature 20°±0·5°C.
Plethysmograph temperature 32°±0·5°C.

Table I shows that in 2 cases there was considerable clinical improvement accompanied by increase in the resting digital temperatures and hand blood-flows. In 3 of the other 4 however was subjective improvement, in that the pain of the attacks was decreased and the intensity of the pallid phase was diminished; but none of them showed any measurable benefit. From this small series it seemed that, although reserpine in this dosage could modify the intensity of initial vasoconstriction by cold, it was not capable of affecting the speed of recovery or the rate of development of a reactionary hyperæmia. Moreover, it was noticed that the metabolic rates of the 2 patients showing considerable benefit were higher than those in whom the improvement was subjective and not confirmed by plethysmography.

TABLE II—EFFECT OF ORAL TRIIODOTHYRONINE 20 μG. Q.D.S. FOR 14 DAYS ON THE RESTING TEMPERATURE OF THE RIGHT INDEX FINGER, HAND BLOOD-FLOWS, AND METABOLIC RATES

Case	Previous sympathectomy	Nutritional lesions	Temperature of right index finger (°C)		Hand blood-flows (ml. per 100 ml. per min.)		Basal metabolic rate (%)	
			Before	After	Before	After	Before	After
7	Yes*	Yes	20·8	32·4	2·7	6·1	22	−3
8	Yes*	Yes	22·4	32·0	3·3	4·9	−16	+1
9	No	No	23·3	33·8	2·9	7·3	− 6	+8
10	Yes*	Yes	21·8	33·8	2·9	6·8	−12	+3
11	No	No	22·3	31·6	3·5	5·2	−17	+8
12	Yes*	No	23·2	31·2	3·4	5·9	−15	+3

Room temperature 20°±0·5°C.
Plethysmograph temperature 32°±0·5°C.
* Vasomotor tone returned.

Pilot Study no. 2

6 cases of primary Raynaud's disease were treated with triiodothyronine 20 μg. q.d.s. In all of them (table II) not only was there an increase in the resting digital temperatures and hand blood-flows but also the cyanotic phase of the attacks was shortened and the rate development of reactionary hyperæmia was extremely rapid. The attacks were either abolished or were short. The patients noticed that if the attacks were induced by severe cold, they were more sudden in onset and more intense than those

TABLE III—REVIEW OF PATIENTS TREATED WITH RESERPINE AND TRIIODOTHYRONINE

Case no.	Age of onset	Previous sympathectomy	Nutritional lesions	Digital temperature of right index finger (°C)		Reserpine (mg. daily)	Triiodothyronine (μg. daily)	Symptoms
				Before	After			
1	Childhood	Yes*	Yes	22·8	34·0	0·5	80	Improved
2	20	Yes	Yes	21·0	34·0	0·5	80	Improved
3	24	No	No	23·3	30·4	0·5	80	Improved
4	15	Yes*	Yes	19·8	33·8	0·25	80	Improved
5	18	No	No	20·4	31·2	0·5	80	Improved
6	33	Yes	Yes	23·2	31·2	0·5	80	Improved
7	32	Yes*	Yes	20·6	23·3	0·5	80†	Failed
8	12	Yes	Yes	21·3	24·6	0·5	80†	Failed
9	20	Yes*	Yes	21·8	31·2	0·5	80	Improved
10	27	No	No	20·2	30·3	0·5	80	Improved
11	40	No	No	22·0	31·0	0·75	100	Improved
12	15	No	No	22·7	22·0	Serpatonil 0·45	80†	Failed
13	28	Yes	Yes	20·9	27·8	0·5	80	Improved
14	23	No	No	21·3	31·6	0·5	60	Cured
15	Teens	No	No	23·8	30·2	0·5	80	Cured
16	40	No	No	22·0	33·8	0·5	80	Improved
17	23	No	No	21·8	31·7	0·5	60	Cured
18	Childhood	No	No	22·3	33·0	10 methoxyd. 10	80	Improved
19	47	No	No	20·8	31·8	0·5	80	Improved
20	28	No	No	22·8	33·2	10 methoxyd. 10	60	Cured
21	19	No	No	20·7	32·8	10 methoxyd. 10	80	Cured
22	Childhood	Yes	No	20·4	25·2	0·5	80†	Failed
23	26	Yes	Yes	21·3	24·2	0·5	80	Failed
24	18	Yes*	No	20·2	27·5	0·5	80	Improved
25	14	No	No	20·5	32·8	0·75	80	Improved
26	28	No	No	20·7	31·3	10 methoxyd. 10	80	Improved
27	26	Yes	No	22·2	33·4	0·5	80	Cured
28	34	Yes	No	21·3	31·6	0·5	80	Cured
29	14	Yes	No	22·7	30·2	0·5	60	Cured
30	38	Yes	No	21·7	32·8	0·5	80	Improved
31	42	No	No	22·2	31·8	0·5	80	Improved
32	29	Yes	Yes	25·2	32·2	0·5	80	Improved
33	29	No	No	23·3	33·0	0·5	80	Improved

Methoxyd. = methoxydeserpidine.
* Stallate ganglionectomy performed after previous excision of T_2 and T_3 sympathetic ganglion.
† Subsequently treated with methylandrostenediol.

previously experienced; but the duration was short and recovery was extremely rapid. In all cases the metabolic rate was increased and it appeared that, as Roth and Sheard had reported, an increase in basal metabolism could shorten the period of recovery from cold restriction, although, if this was severe enough, an apparently increased initial vasoconstriction could temporarily overcome the higher resting hand blood-flows.

The observations on these drugs suggested that whereas the main action of reserpine was to modify the initial vasoconstriction response to cold, triiodothyronine, by increasing the tissue metabolism, could lessen the duration of constriction and increase the rate of recovery.

Clinical Trial of Reserpine and Triiodothyronine

From these observations it seemed possible that reserpine and triiodothyronine, given together, might influence not only the degree of initial vasoconstriction in Raynaud's disease but also the rate of recovery. During the past four years (table III) 33 cases have been treated in this way. 16 had had previous upper-limb sympathectomies and all of these had relapsed with evidence of return of sympathetic nervous control of the hand blood-vessels. 5 had had further bilateral sympathectomies without any long-term benefit. In 10 cases nutritional lesions of digits, either healed or unhealed, were present, and in 1 case a digit had been amputated for gangrene.

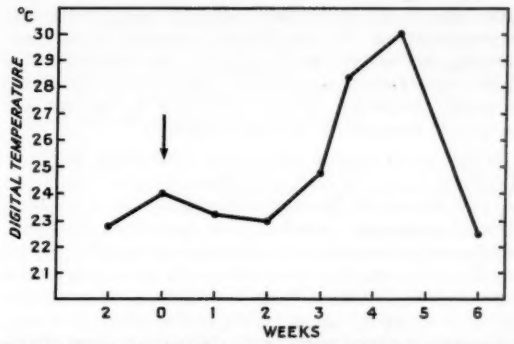
The results were on the whole extremely gratifying and were superior to those of any of the previous treatments. In 8 patients no further attacks of pallor or cyanosis occurred. In 20 the frequency and intensity of the attacks were considerably reduced, pain was relieved, and the duration of cyanosis was shortened from hours to minutes. In 5 there was no response to treatment.

Experiments with various dosage indicated that in most cases the optimum dose of reserpine was 0·25 mg. b.d. and triiodothyronine 20 μg. q.d.s. Increasing the dosage of reserpine was without value and in some cases appeared to block the increase in peripheral tissue metabolism induced by triiodothyronine. Increasing the dose of triiodothyronine above 80 μg. was followed by cardiac acceleration but no increase in metabolism.

The effect on the resting pulse-rate was variable; in some cases the bradycardia normally found in patients treated with reserpine was evident, whilst in others there was a moderate increase to a rate of 80 per minute. The diastolic blood-pressure was usually decreased by 10 mm. Hg and the pulse increased, the increase in the force of the pulse beat being clinically obvious. In patients whose symptoms were improved or cured, the increase in subjective warmth was remarkable; the cold sensitivity was abolished and the general mental outlook changed from that of a cold, sometimes miserable and introverted person whose life was in many ways governed by feeling perpetually cold, to one who no longer feared cold and whose activities both in the home and outside were therefore increased. In some cases digital ulcers which had been present for years healed and remained healed.

Side effects were slight. A third of the patients had a period of tiredness lasting ten to fourteen days, but in all but 2 this required no modification of treatment. In these 2 cases 'Serpatonil',* and more recently 10-methoxy-deserpidine, were substituted for reserpine: in dosages of 0·45 mg. and 10 mg. daily, respectively, they have eliminated depressive side-effects. Apart from this early tiredness, no patient had any period of mental depression,

* Serpatonil=0·15 mg. reserpine and 5 mg. phenyl-(*d*-piperidyl)-acetic acid methyl ester hydrochloride (Ciba).



Primary Raynaud's disease (case 22). Effect of 250 mg. testosterone œnanthate intramuscularly on resting temperatures of right index finger. Patient maintained on reserpine 25 mg. b.d., and triiodothyronine 20 μg. q.d.s. Room temperature 20±0·5°C.

although 1 stated that he could not perform intricate calculations so rapidly. Diarrhœa, occurring in 2 cases, stopped as soon as the dose of reserpine was decreased by 0·25 mg. There were no signs or symptoms of cardiac strain. The menstrual cycle remained unchanged in all patients in whom it was previously normal. There was no constant pattern of change in either the weight or the appetite of these patients.

The Failures with Reserpine and Triiodothyronine

4 of the 5 patients who failed to respond to reserpine and triiodothyronine had nutritional lesions of the fingers and had had previous upper-limb sympathectomies. In these patients, sympathetic nervous control of the hand vessels had returned, and further digital ulceration had occurred since the original sympathectomy. Reserpine and triiodothyronine did not change the resting digital temperatures or hand blood-flows, and the patients remained sensitive to cold. Evidently there had been no increase in the general level of tissue metabolism, and increase of the dosage of triiodothyronine merely induced cardiac acceleration.

When the endocrine features of these cases were reviewed and compared with those in whom an increased tissue metabolism was allied to improvement in the digits, the only significant difference lay in the lower level of excretion of the urinary 17-ketosteroids in the failed group of patients. Numerous authors have pointed out that, in people with diminished androgen activity, metabolism increases considerably during treatment with testosterone propionate or methyl testosterone (Kenyon 1938, Kenyon et al. 1940, McCullagh and Rossmiller 1941). Moreover, Jones et al. (1941) have found that such patients often have decreased circulation-times although their pulse-rates and blood-pressures are unchanged.

In view of the low 17-ketosteroid excretion levels it was thought possible that in these unsuccessful cases an increase in tissue metabolism might be induced by androgens.

Clinical Trial of Androgens

A single intramuscular injection of 250 mg. testosterone œnanthate was given to 4 of the 5 patients whilst maintaining them on reserpine 0·25 mg. b.d. and triiodothyronine 20 μg. q.d.s. A significant increase in their resting digital temperatures occurred in all 4 between the second and fourth weeks (see figure) together with a feeling of bodily warmth. There was no significant change in the

pulse-rate or blood-pressure. In all cases there was improvement in the peripheral vascular symptoms, including the degree and character of cyanosis. The digital temperatures returned to their low levels within six weeks of the date of injection. The 5th patient was not treated because she became pregnant.

At first it was thought inadvisable to continue this form of therapy in women, mainly because of the virilising effect and suppression of the menstrual cycle. Less virilising anabolic androgens, however, have now been developed and a trial has been made of methylandrostenediol, which has the advantage that it can be given by mouth. All 4 patients who benefited from testosterone showed considerable improvement on methylandrostenediol 50 mg. b.d.—later reduced to 50 mg. daily in 2 cases where menstruation became irregular. The clinical improvement was accompanied by an increase in general bodily warmth which started usually in two to three weeks. The improvement, moreover, was progressive over many months as an improved peripheral blood-flow influenced the general nutrition of the hands and digits.

Discussion

Although at first the action of reserpine was thought to be mainly central, by depression of the sympathetic outflow from the hypothalamus (Bein 1955), more recently Muscholl and Vogt (1958) have shown that reserpine causes a generalised loss of catechol amines throughout the body, and Burn and Rand (1958) have found that the noradrenaline content of arteries is similarly decreased. The use of reserpine in Raynaud's disease and Buerger's disease has previously been reported by Scalfi et al. (1956) and Reichert (1956), but experience suggests that dramatic improvement of symptoms is most likely in cases of peripheral vascular disease where the tissue metabolism is already high. Reserpine, by itself, apparently does not induce any considerable increase in blood-flow where the peripheral vascular systems are part of a generalised cold sensitivity and hypometabolic state

To raise tissue metabolism as a means of overcoming peripheral vasoconstriction is justifiable only where a reserve of blood-flow can meet the increased needs of the tissues. It would be quite wrong to apply this form of therapy to an ischæmic lesion which had arisen entirely from organic arterial obstruction. In Raynaud's disease, although structural disease of the digital vessels is often present (Peacock 1958), it is rarely the sole cause of nutritional lesions of the digits. In most cases ulcers arise during the winter months as the result of a cold constrictor reflex which is superimposed upon pre-existing structural disease, and such ulcers often heal as the environmental temperature rises. When investigated plethysmographically under conditions which induce vasodilatation, the hand blood-flows can always be increased (Peacock 1958). There is a reserve of blood-flow which is more than adequate to maintain digital nutrition, although vasospasm has prevented it from being utilised.

It was appreciated that in using a thyroid hormone such as triiodothyronine to increase tissue metabolism, an associated increase in peripheral sympathetic tone might be induced. This possibility was evident not only from the work of Spinks (1952), who showed that thyroid decreased the amine oxidase content of arterial walls, but also from the demonstration by Smith (1953) that, in vitro, thyroxine potentiates adrenaline-induced vasoconstriction of isolated arteries. In the cases of Raynaud's disease treated with triiodothyronine any increase in sympathetic tone was apparently masked, in most circumstances, by the higher resting hand blood-flows: only under conditions of severe cold did attacks of vascular spasm cause digital pallor. It was noteworthy, however, that although the number and duration of the attacks were decreased, they were more rapid in onset and of greater intensity.

The action of reserpine in controlling this aspect of of Raynaud's phenomenon recalls the observation of Canary et al. (1957) that when thyrotoxic patients were treated with reserpine many of the signs attributable to sympathetic overaction were diminished, although the metabolic state of the patients remained high.

Why androgen therapy should increase metabolism is not clear. Clinically it seemed to sensitise the patients to the metabolic action of triiodothyronine, and its effect was similar to that observed with testosterone by Eidelsburgh and Ornstein (1940).

As a result of the above investigations, it has proved possible to establish a practical form of treatment for patients with Raynaud's disease which does not entail detailed medical investigation. This treatment is, moreover, of particular value in cases where relapse has followed sympathectomy, with signs of a return of vasomotor control of the hand blood-vessels.

Patients are initially treated with 10-methoxydeserpidine 5 mg. b.d. for two weeks; and this alone will sometimes cause considerable improvement. If improvement is absent or slight, triiodothyronine 20 µg. q.d.s. is added for a further two weeks. In most cases there will then be both subjective and objective evidence of increased peripheral blood-flow and a decrease in general sensitivity to cold. At this stage it may be necessary to adjust the dosage of these compounds according to changes in pulse-rate, residual cyanosis, and degree of clinical improvement. In cases where cold intensity persists, methylandrostenediol 50 mg. b.d. is added and the case is reviewed after a further four weeks. Failure to respond to this therapy would then be regarded as an indication for inpatient investigation. In many cases the dosage of triiodothyronine can be gradually reduced during the summer months, and patients should be advised to cease therapy if there is any possibility that they are pregnant.

Although this form of therapy cannot be regarded as more than a first step towards the treatment of this disease by changing the tissue metabolism, it has proved useful in many cases where no other form of therapy has been satisfactory.

Summary

Observations and experiences in the treatment of primary Raynaud's disease of the upper limb are summarised. Reserpine, triiodothyronine, and in some cases methyl androstenediol, have been used in the treatment of 33 patients over a period of four years.

A course of treatment for outpatients is proposed.

REFERENCES

Barcroft, H., Hamilton, G. T. C. (1948) *Lancet*, ii, 770.
Bein, H. J. (1955) *Ann. N.Y. Acad. Sci.* **61**, 4.
Burn, J. H., Rand, M. J. (1958) *Lancet*, i, 903.
Canary, J. J., Schaaf, M., Duffy, B. J., Kyle, L. H. (1957) *New Engl. J. Med.* **257**, 435.
Eidelsburgh, J., Ornstein, E. A. (1940) *Endocrinology*, **26**, 46.
Felder, D. A., Simeone, F. A., Linton, R. R., Welch, C. E. (1949) *Surgery*, **26**, 1014.
Freedberg, A. S., Kurland, G. S., Hamolsky, W. (1955) *New Engl. J. Med.* **253**, 57.
Hunter, J. I. (1924) *Surg. Gynec. Obstet.* **39**, 721.
Jones, R., McCullagh, E. P., McCullagh, D. R., Buckaloo, G. W. (1941) *J. clin. Endocrin.* **1**, 656.

References continued at foot of next column

ROLE OF INTERFERON IN RECOVERY FROM VIRUS INFECTIONS

ALICK ISAACS
M.D. Glasg.

GRISELDA HITCHCOCK
B.A. Cantab.

From the National Institute for Medical Research, Mill Hill, London, N.W.7

THE question which prompted the present studies is: What factors are important in recovery from virus infections? The first factor which springs to mind is viral antibody. But while there can be no doubt of the key role of viral antibody in resistance to second and subsequent infections, its role in recovery from a first infection by a virus is in some doubt. Viral antibody often appears very late in an infection in relation to the time at which recovery starts, and its appearance in high titre in the blood-stream may be a rather inappropriate response to a virus which infects the respiratory tract where antibody appears in only very low concentration (Fazekas de St. Groth and Donnelley 1950). It is known that cells infected with viruses in tissue culture may, in the absence of antibody formation, reach a stage of chronic infection—a state of equilibrium which has been shown in some cases to be due to acquisition of cellular resistance to virus infection. Cellular resistance to virus infections in vitro seems in some cases to be mediated by the production of interferon by the infected cells (Ho and Enders 1959, Henle et al. 1959), and in the present investigation we have studied its production in vivo during the course of infection of mice with influenza virus.

Interferon was first detected following treatment of cells with inactivated influenza viruses (Isaacs and Lindenmann 1957). Subsequently it was shown to occur at a late stage of infection of cells in vitro by live influenza virus (Tyrrell 1959, Burke and Isaacs 1958), in rabbits infected intradermally with vaccinia virus (Nagano and Kojima 1958), and in fertile hens' eggs infected with influenza virus (Wagner 1960). Substances with similar properties to interferon have also been detected following infection of cells in vitro with poliomyelitis (Ho and Enders 1959), vesicular stomatitis (Cooper and Bellett 1959), tick-borne encephalitis (Vilcek 1960), and parainfluenza (Chany 1960) viruses. The role of interferon as a factor in cellular resistance to virus infections is therefore of some interest.

Materials and Methods

Mice of about 15 g. were infected intranasally under light ether anæsthesia with 0·05 ml. of the PR8 strain of influenza virus A diluted as described in the text. Uninfected mice served as controls. At intervals after infection groups of 3 mice were killed, bled out, and their lungs removed. Extracts of the pools of lungs (1 ml. of buffered saline to each pair of lungs) and sera were titrated for their content of virus, viral antibody, and interferon.

Titration of Virus

Tenfold dilutions of virus were prepared in 50% Hartley broth in saline. 0·05 ml. volumes were inoculated allantoically into groups of four 10-day fertile hens' eggs which were incubated for 3 days at 35°C and then tested for their virus content, using the presence of hæmagglutinin as an index of virus growth. The 50% infectivity end-point ($I.D._{50}$) is the dilution which infects 50% of inoculated eggs.

Titration of Antibody

Sera were treated with trypsin to remove normal inhibitors of hæmagglutination and were then titrated for their content of antihæmagglutinin to the PR8 virus by the methods described in the World Health Organisation (1953) report.

Titration of Interferon

In order to avoid confusion with viral antibody the interferon content of lung extracts was titrated with an antigenically unrelated virus. The lung extracts were first dialysed overnight at 2°C at pH2 in order to destroy virus without affecting the interferon concentration (Lindenmann, Burke, and Isaacs 1957) and then dialysed back to pH 7·4 before test.

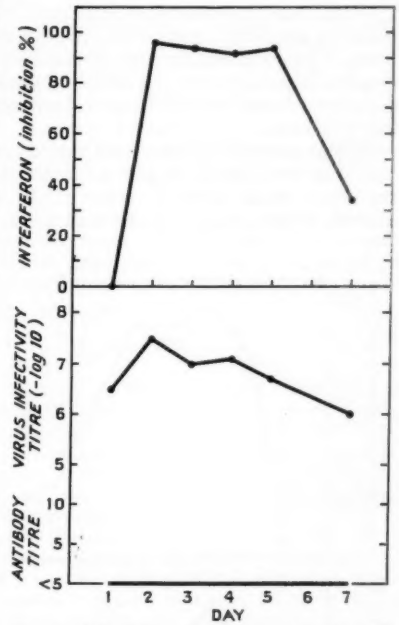


Fig. 1—Infectivity, interferon content, and antibody content of lungs of mice killed at intervals after infection with 600 $I.D._{50}$ of PR8 virus.

The technique used to titrate interferon is similar to that described by Wagner (1960). Primary cultures of mouse-embryo fibroblasts, after about a week's cultivation in vitro in a medium containing 10% calf-serum and 0·5% lactalbumin hydrolysate, were used to prepare secondary cultures in 4 cm. petri dishes containing about 2 million cells each. After 24 hours' incubation the media were removed and replaced by 2 ml. of a 1 in 2 dilution of lung extract. After overnight incubation at 37°C this was removed and replaced by 0·5 ml. of encephalomyocardia virus diluted so as to give about 50–100 plaques in each dish. After incubation for 1 hour to allow the virus to be adsorbed to the cells the fluid was removed and replaced by 3·5 ml. of overlay containing 0·9% agar mixed with nutrient medium. The plates were now incubated for 48 hours at 37°C, stained with 1 ml. of a 0·05% neutral-red solution for 1 hour at 37°C, and the plaques were then counted.

The interferon content is expressed in figs. 1 and 2 as the percentage inhibition of the virus-plaque count. Reliance on

MR. PEACOCK: REFERENCES—*continued*

Kenyon, A. T. (1938) *Endocrinology*, **23**, 121.
— Knowlton, K., Sandiford, I., Koch, F. C., Lotwin, G. (1940) *ibid.* **26**, 26.
Kurland, G. S., Hamolsky, M. W., Freedberg, A. S. (1955) *J. clin. Endocrin.* **15**, 1354.
Landis, E. M., Gibbon, J. H. (1933) *Arch. intern. Med.* **52**, 785.
McCullagh, E. P., Rossmiller, H. R. (1941) *J. clin. Endocrin.* **1**, 503.
Muscholl, E., Vogt, M. (1958) *J. Physiol.* **141**, 132.
Peacock, J. H. (1958) *Clin. Sci.* **17**, 575.
— (1959) *Circulation Res.* **7**, 821.
Raynaud, A. G. M. (1862) De l'Asphyxie locale et de la gangrène symetrique des extrémitiés. Thèse de Paris.
Reichert, F. L. (1956) *Amer. J. Surg.* **91**, 41.
Robertson, C. W., Smithwick, R. H. (1951) *New Engl. J. Med.* **245**, 317.
Ross, J. P. (1935) *Brit. J. Surg.* **23**, 433.
Roth, G. M., Sheard, C. (1950) *Circulation*, **1**, 1142.
Royle, N. D. (1924) *Med. J. Aust.* i, 77.
Scalfi, L., Jacono, A., Iuliani, G. (1956) *G. Clin. med.* **37**, 1635.
Simmons, H. T., Sheehan, D. (1939) *Brit. J. Surg.* **27**, 234.
Smith, D. J. (1953) *Amer. J. Physiol.* **172**, 118.
Smithwick, R. H., White, J. C. (1946) The Autonomic Nervous System. London.
Spinks, A. (1952) *J. Physiol.* **117**, 35P.
Tittle, C. R. (1956) *J. Amer. med. Ass.* **162**, 271.

the number of plaques alone will lead to a slight underestimate of interferon activity, since, in an assay of this kind, interferon reduces both the size and the number of plaques. A rough correlation has, however, been found between the percentage inhibition of the plaque count and the dilution of a preparation of interferon, and this forms the basis of the present method.

Results

Mice were infected with 600 egg infective doses ($I.D._{50}$) of the PR8 strain of influenza virus, and the virus and interferon content of their lungs and the antibody content of their lungs and sera were measured at intervals thereafter. The results are plotted in fig. 1.

The virus concentration in the lungs rose rapidly to a peak but decreased only very slowly thereafter. Interferon was not detectable on the 1st day after infection, but it soon increased in amount, falling off at about the 7th day. 600 $I.D._{50}$ is quite a large dose of this virus, and the animals began to die on the 7th day. No antibody was demonstrable in the lungs or sera up to the 7th day.

In a second similar experiment, mice were infected with 60 $I.D._{50}$ of the same virus. The results are plotted in fig. 2.

In this experiment the virus titre rose sharply to a peak and then decreased more rapidly than in the first experiment. The interferon followed the rise in virus titre quite closely. The mice survived for 10–12 days and antibody was demonstrated in their lungs and sera on the 11th day, but not before.

Further experiments were then carried out with inoculation of 20 $I.D._{50}$ and 6 $I.D._{50}$ of the same virus, in order to see what would happen under conditions when the animals would recover. In animals which were killed it was noticed that about 10–20% of the lungs were consolidated but in each animal most of the lung was macroscopically healthy, whereas in animals which died after administration of the larger doses of virus the lungs showed almost complete consolidation.

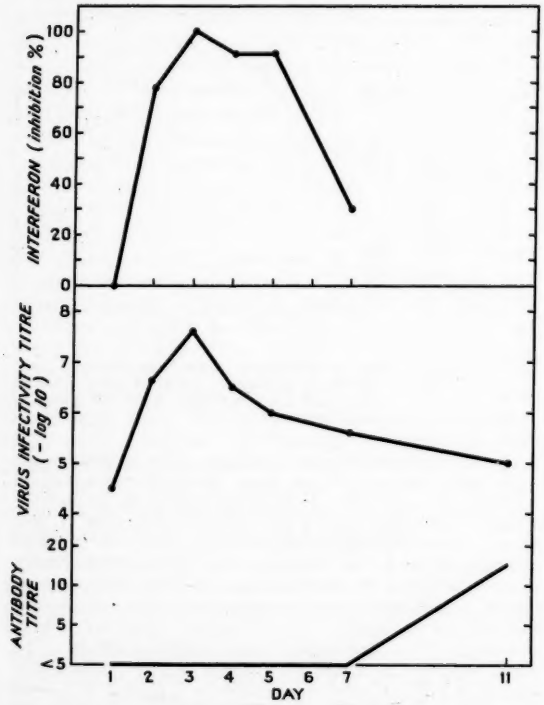


Fig. 2—Infectivity, interferon content and antibody content of lungs of mice killed at intervals after infection with 60 $I.D._{50}$ of PR8 virus.

APPEARANCE OF VIRUS, ANTIBODY, AND INTERFERON AFTER INFECTION WITH DIFFERENT DOSES OF INFLUENZA VIRUS

Experiment no.	Dose of virus inoculated ($I.D._{50}$)	Peak of virus in the lungs	Time of peak of interferon in the lungs (days)	Antibody first detected in lungs and sera (day)	Time at which mice died (day)
1	600	$10^{7.6}$ on 2nd day	2nd–5th	None found by 7th	7th
2	60	$10^{7.7}$ on 3rd day	3rd	11th	10th–12th
3	20	$10^{8.5}$ on 3rd and 5th days	3rd–5th	14th	All survived
4	6	$10^{8.5}$ on 3rd day	3rd–5th	14th	All survived

The results of the main points of these experiments are summarised in the accompanying table.

It is striking that in each case the titre of virus had begun to decrease some days before antibody was demonstrable, but at a time when interferon was present in the lungs in high titre. It was also interesting to find that interferon was demonstrable in the lungs of mice infected with a very large dose of an avirulent influenza virus (10^6–10^7 $I.D._{50}$ of strain Kunz), from which the animals readily recovered.

The evidence that the protective substance in mouse lungs is in fact interferon comes from a comparison of its properties with those of interferon prepared in chick or mouse embryo cells in vitro. The interferon extracted from mouse lungs was non-dialysable, stable at pH2, not sedimented after centrifugation at 100,000 G for 4 hours, not neutralised by influenza viral antiserum, and was inactivated by incubation with 0·001% pepsin for 1 hour at 37°C. In all these properties it closely resembled chick interferon but it was distinctly more labile to heat than chick interferon, being largely inactivated after heating at 60°C for 1 hour. In addition it showed antiviral activity when tested in mouse cells but not in chick cells. In these last two properties it resembled interferon prepared from mouse cells in vitro, and differed from interferon prepared in chick cells.

Discussion

In these experiments, three factors which might limit virus production and thus aid in the animals' recovery have been considered.

The first factor is the availability of susceptible cells. Here the experiments show that, when 60 or 600 $I.D._{50}$ of virus was used, the virus multiplied until the lungs were completely consolidated and the animals eventually died. But when 6 or 20 $I.D._{50}$ of virus was inoculated the virus multiplied to only a limited extent and the animals survived with consolidation involving only about 10–20% of their lungs. Clearly the availability of cells cannot be the factor which limits virus multiplication.

The second factor considered was the development of viral antibody. The present experiments show that antibody was first detected more than a week after the peak of virus growth had been reached. Fazekas de St. Groth and Donnelley (1950) found that traces of antibody were first demonstrable in the serum of mice 8 days after intranasal infection with a small dose of the MEL strain of influenza virus which produced 8% lung consolidation—a result which is in good agreement with

the present findings. When, however, a very large dose of virus (200 million times the dose given intranasally) was inoculated intraperitoneally into mice, serum antibody could be demonstrated after 3–5 days. Fazekas and Donnelley suggested that, after intranasal infection with a small dose of virus, antibody might be produced on the 3rd–4th day and combine with virus in the lungs. In their view it is only when excess antibody is produced, over and above that required to neutralise virus in the lungs, that antibody can be demonstrated in the serum. In the present experiments the amount of virus produced after inoculation of 6–20 I.D.$_{50}$ of virus was less than a hundredth of that produced after inoculation of 60 I.D.$_{50}$ of virus and should have therefore provided a very much smaller antigenic stimulus. But the virus titre had begun to decline after the 5th day, while antibody was not demonstrable until the 14th day. Our results are therefore not easily reconciled with (although they do not exclude) the hypothesis of Fazekas and Donnelley, which is indeed very difficult to prove or to disprove. The hypothesis was originally required, however, in order to account for recovery from virus infections by means of antibody alone, and this difficulty no longer exists.

The experiments described here show, in fact, that relatively high concentrations of interferon are present in the lungs, at the right place and at the right time to account for the recovery from influenzal infection in mice. From earlier work (Isaacs and Lindenmann 1957) it is known that interferon, like antibody, diffuses freely out of cells so that it could, in theory, diffuse out to protect cells in the neighbourhood of the infection. What these experiments do not reveal is the size of the contributions of viral antibody, interferon, and other factors to recovery from virus infections; but it could be imagined that antibody would play a more significant part in infections in which viræmia is important in pathogenesis, whereas cellular resistance (by interferon and other factors) might be more important in infections of the respiratory tract and other surface infections. The fact that patients with hypogammaglobulinæmia may recover normally from many virus infections without producing any detectable antibody should give us an opportunity to assess anew the role of these factors in the recovery from virus infections in man.

Summary

Mice were infected intranasally with different doses of influenza virus and their lungs and sera were studied for their content of virus, viral antibody, and interferon. The interferon content of their lungs followed closely the peak of virus titre, but antibody was not detected in their lungs and sera until at least a week later. It is concluded that interferon may play a significant role in the recovery of mice from influenza-virus infection.

We should like to thank Dr. C. H. Andrewes, F.R.S., for his advice and criticism, and Mr. V. G. Law and Miss V. Coker for their most valuable technical help.

REFERENCES

Burke, D. C., Isaacs, A. (1958) *Brit. J. exp. Path.* **39**, 452.
Chany, C. (1960) *C.R. Acad. Sci. Paris*, **250**, 3903.
Cooper, P. D., Bellett, A. J. D. (1959) *J. Gen. Microbiol.* **21**, 485.
Fazekas de St. Groth, S., Donnelley, M. (1950) *Aust. J. exp. Biol. med. Sci.* **28**, 45.
Henle, W., Henle, G., Deinhardt, F., Bergs, V. V. (1959) *J. exp. Med.* **110**, 525.
Ho, M., Enders, J. F. (1959) *Proc. nat. Acad. Sci.* **45**, 385.
Isaacs, A., Lindenmann, J. (1957) *Proc. roy. Soc. B*, **147**, 258.
Lindemann, J., Burke, D. C., Isaacs, A. (1957) *Brit. J. exp. Path.* **38**, 551.
Nagano, Y., Kojima, Y. (1958) *C.R. Soc. Biol., Paris*, **152**, 1627.
Tyrrell, D. A. J. (1959) *Nature, Lond.* **184**, suppl. 7, p. 452.
Vilcek, J. (1960) *ibid.* **187**, 73.
Wagner, R. R. (1960) *Bact. Rev.* **24**, 151.
World Health Organisation (1953) *Wld Hlth Org. tech. Rep. Ser.* no. 64.

SHEEP AS A POTENTIAL RESERVOIR OF TOXOPLASMA FOR MAN

P. C. C. GARNHAM
M.D., D.Sc. Lond., D.P.H.
PROFESSOR OF MEDICAL PROTOZOOLOGY IN THE UNIVERSITY OF LONDON

R. LAINSON
Ph.D. Lond.
LECTURER IN PARASITOLOGY

From the Department of Parasitology, London School of Hygiene and Tropical Medicine, London, W.C.1

SHEEP have been incriminated as a source of infection with *Toxoplasma gondii* on several occasions recently.

Cole et al. (1954), in the United States, isolated the organism and studied its behaviour in pregnant ewes, which not only became ill but gave birth to lambs in which the disease was widespread. Hartley and Marshall (1957) described cases of abortion in sheep in New Zealand, which proved to be the result of infection with *T. gondii*; the organism was isolated and inoculated into pregnant ewes, which gave birth to infected lambs. Beverley and Watson (1959) demonstrated the organism in the brain or liver in six out of nine abortions in sheep in Yorkshire. de Roever-Bonnet (1957) detected cytoplasm-modifying antibodies by the dye test in eight out of twenty-three sheep in Amsterdam. Rawal (1959) found that 11% of one sample, and 21% of a second sample, of sheep were positive to the dye test in Sheffield, and he isolated six strains of the organism from them. Rawal nevertheless thinks that eating undercooked infected mutton plays little part in transmitting the disease to man, because the incidence was similar in vegetarians and meat eaters. Hartley and Marshall (1957) observed toxoplasma cysts in the hearts of artificially infected sheep.

The role of mutton in transmitting the disease to man has been little considered, however, while the actual course of infection in sheep has not been related to edible material. Accordingly, we studied experimental toxoplasma infections in sheep.

Experiments

Material and Methods

The obvious choice of a toxoplasma strain would be one isolated from a naturally infected sheep. Fortunately we were able to obtain such a strain through the courtesy of Prof. R. P. Beattie of the University of Sheffield. The parasite was well adapted, giving rise to chronic symptomless infections in sheep and mice, and was well suited therefore for studying the normal course of toxoplasmosis in sheep.

Our six experimental lambs were of the " Dorset shorthorn " breed, and were obtained, when 10 weeks old, on Feb. 2, 1959. To avoid possible infection from outside sources they were housed in fully enclosed concrete pens at our field station at Winches Farm, Hertfordshire, and were given a balanced standard diet without natural grasses.

Serum specimens from the animals were tested by the Sabin-Feldman dye reaction for toxoplasma, as modified by Beverley and Beattie (1952); all specimens were inactivated at 56°C for 20 minutes before testing.

The parasite was isolated from sheep tissues by triturating the material in sterile physiological saline, and inoculating 1 ml. of the suspension into pairs of multimammate rats (*Mastomys coucha*) by the intraperitoneal route. Rats were used in preference to laboratory mice because they are more susceptible to infection by toxoplasma. In multimammate rats avirulent strains of the parasite may produce fulminating and fatal infections, while in mice they produce only symptomless infections when the parasite is often difficult to detect (Lainson 1955). A week after inoculation the multimammate rats were killed, and the peritoneal exudates were examined for toxoplasma after staining with Giemsa's stain. Negative exudates were passaged into pairs of mice: a week later one mouse of each pair was killed and examined in the same way, while the

DYE TEST TITRES AND TISSUE EXAMINATIONS OF 6 SHEEP

Weeks after infection	2	4	6	8	10	12	14	16	37
Sheep I (uninfected control)	1/4 (negative)	1/1 (negative)	1/1 (negative)	1/4 (negative)	1/1 (negative)	1/4 (negative)	No test	1/4 (negative)	1/16 s† (negative)
Sheep II (intraperitoneal inoculation)	1/256	1/256*	1/1024	1/256	1/64	1/256	,, ,, *	1/128 s*	..
Sheep III (intravenous inoculation)	1/256	1/1024*	1/256	1/1024	1/64	1/512	,, ,, *	1/128 s*	..
Sheep IV (intravenous inoculation)	1/256	1/1024*	1/1024	1/256	1/64	1/1024	,, ,, *	1/256	1/800 s*
Sheep V (oral inoculation)	1/1	1/16	1/4	1/4	1/1	1/16	,, ,,	1/4 s†	..
Sheep VI (inhalation)	(negative) 1/4	1/256†	1/256	1/16	1/16	1/512	,, ,, †	1/128 s*	..

s = Sheep killed for examination. * = Toxoplasma present in muscle. † = Muscle apparently free of toxoplasma.

other mouse was usually left for a month or more before its brain was examined for toxoplasma cysts.

Tissues for sectioning were fixed in aqueous Bouin's fluid or in formal saline; serial sections were cut at 4 μ, and stained with hæmatoxylin and eosin.

Biopsy specimens were taken of thigh muscle from the sheep, using procaine as a local anæsthetic. Pieces of muscle measuring about $2 \times 2 \times 2$ cm. were removed; half were fixed for sectioning and the rest were triturated for passage into the multimammate rats.

Experimental Infection of Sheep

Initial dye tests (see table) showed that none of the sheep had antibodies against toxoplasma. The following experiments were begun on March 10, when the sheep were 15 weeks old.

Sixteen mice had been infected with the sheep strain of toxoplasma 6 weeks previously. Their brains were removed, pooled, and gently triturated in physiological saline. The number of cysts was estimated at about 300 per ml. of suspension. The sheep were then infected with this suspension:

Sheep I.—Control animal. No inoculation. Kept in complete isolation from other sheep.

Sheep II.—Received 3·5 ml. of brain suspension by the intraperitoneal route.

Sheep III and IV.—Each received 3·5 ml. intravenously.

Sheep V.—Given 3·5 ml. of the suspension by mouth.

Sheep VI.—Given 3·0 ml., after dilution to 50 ml. with further saline, by fine spray into the throat. Spraying was continued for 4 minutes, using an aerograph-type spray.

At the same time as the sheep were inoculated, the suspension was introduced into the peritoneal cavity of four multimammate rats and four white mice, to check the viability of the organisms.

Dye tests were made on serum from the sheep at fortnightly intervals for 12 weeks. Final dye tests were made when the sheep were killed for detailed examination of tissues.

Muscle biopsy specimens were taken 24 and 79 days after inoculation only from those sheep which developed significant titres. The muscle was also examined when the sheep were killed.

Results

Behaviour of the Strain in Rats and Mice

Three of the four multimammate rats, inoculated with 0·2 ml. of the infected mouse-brain suspension, died 7 days later from acute toxoplasmosis. The fourth rat was killed on the 9th day, and it appeared to have been recovering. Passage of peritoneal exudate from the rats into mice showed the newly acquired virulence to be retained, the mice dying in 6–8 days.

None of the four mice inoculated at the same time as the multimammate rats developed symptoms, and the usual chronic infection ensued. In view of the greater susceptibility of *M. coucha* to this sheep strain of toxoplasma, we used these rats in all later attempts to isolate the parasite from sheep tissues.

Dye Tests in Exposed Sheep

Four experimental sheep promptly developed antibody titres. These sheep were inoculated by the intraperitoneal (II) and intravenous routes (III and IV), and by spray into the throat (VI). The control sheep (I) showed no significant rise in titre, while the lamb fed with the inoculum (V) showed only transient titres of 1/16 twice . The course of antibody production is shown in the table; it will be noted that as late as 10 months after infection the titre was still 1/800.

Toxoplasma in Skeletal Muscle

Toxoplasma was isolated 24 and 79 days after infection from muscle biopsy specimens from sheep II, III, and IV. Although very large numbers of muscle sections were examined, only two cysts were found (in the muscle from sheep III on the 24th day). The larger cyst, measuring 50 $\mu \times 25$ μ, showed the usual distortion caused by residence in a contractile muscle-cell (fig. 1). Passage of triturated muscle into multimammate rats proved positive in all these instances. Toxoplasma could not be isolated or demonstrated in the muscle taken from sheep VI at the same times.

Toxoplasma in the Sheep's Organs

Although we had established the presence of toxoplasma in the skeletal muscle of three sheep, 24–79 days after their intraperitoneal or intravenous inoculation, it was still desirable

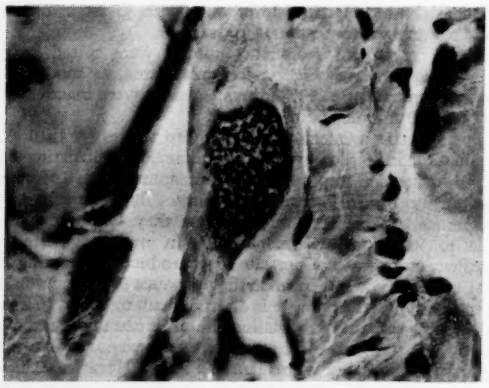


Fig. 1—Cyst of *Toxoplasma gondii* in muscle of sheep III 24 days after inoculation. (×500.)

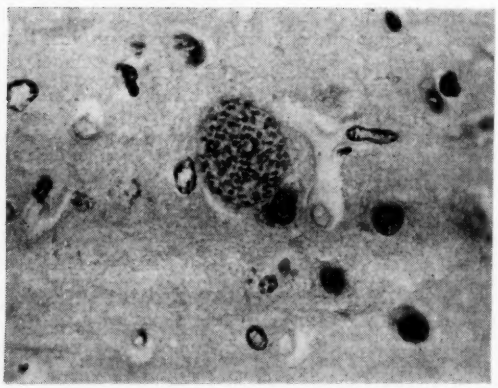


Fig. 2—Section of cyst of *Toxoplasma gondii* in brain of sheep III 16 weeks after inoculation. (×500.)

to determine what other edible parts were affected. We also wished to examine sheep VI more thoroughly, for this animal possessed a high dye-test titre, although attempts to isolate toxoplasma from its muscle had failed.

Accordingly, 112 days after their inoculation, sheep II, III, and VI were killed and parts of the brain, skeletal and heart muscle, liver, kidney, thymus gland, and lung of each were inoculated into multimammate rats. The first five of these tissues are predominantly eaten by man, while the thymus gland is less regularly sold in the butcher's shop as "sweetbread". Lung is not normally considered edible, but toxoplasma cysts have been found in the lungs of mice, rabbits, and a dog (Lainson 1955), and the "lights" of cattle and sheep are regularly used as food for dogs.

Toxoplasma was isolated from tissues, thus:

Sheep II (intraperitoneal inoculation).—Brain, skeletal muscle, heart-muscle, liver.

Sheep III (intravenous inoculation).—Brain, skeletal muscle, heart-muscle, kidney.

Sheep VI (toxoplasma sprayed into throat).—Brain, skeletal muscle.

All isolations of the parasite were made in the first passage to multimammate rats. One cyst (fig. 2), found in a section of brain from sheep III, measured 30 μ in diameter. This corresponds to an age of 16 weeks' infection.

Hazards of Infected Meat

The presence of toxoplasma cysts in the skeletal muscle of these sheep, at least as early as 24 days and as late as 79 days after the animals had been infected, points to certain hazards. Although lamb and mutton are not deliberately eaten raw, undercooked meat might prove a source of infection.

A whole leg from sheep III was heated in an electric oven for 40 minutes at a low temperature. When the leg was cut open, much of the flesh around the bone was found to be completely uncooked although it was hot. A piece of uncooked flesh, about 2 c.cm. in size, was excised, triturated in sterile physiological saline, and inoculated into a pair of multimammate rats. Toxoplasma could not be isolated from this material despite two further subinoculations in mice.

Ten multimammate rats were starved for 24 hours, and were then fed on coarsely minced skeletal muscle from sheep II and III. Examination later showed that two of the ten rats had become infected with toxoplasma. This shows that oral transmission of the sheep strain of toxoplasma from eating uncooked meat is inconstant but possible.

Persistence of Infection in Sheep

Three sheep remained from our original experiment—namely sheep V (attempted infection by the oral route), sheep IV (known to be infected by the intravenous route), and sheep I (the control, with consistently negative dye tests). Of these, sheep V was killed on Aug. 10, 5 months after the experiment was started. Brain and skeletal muscle were passaged into multimammate rats, and toxoplasma could not be isolated. Because the dye test on the serum of this sheep remained negative, we concluded that giving toxoplasma cysts by mouth had failed in this instance to produce infection.

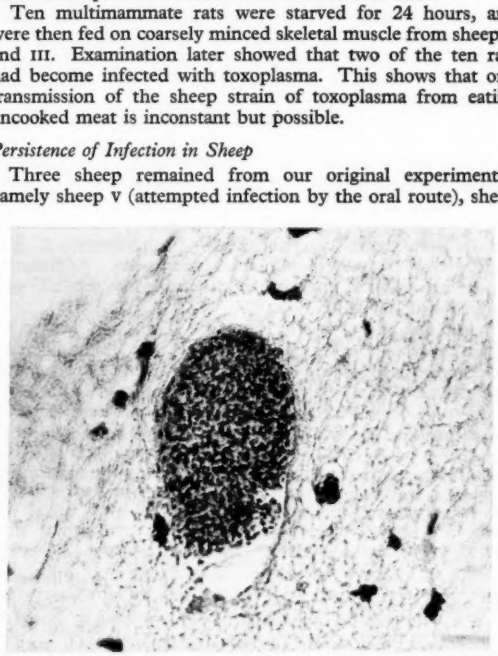


Fig. 3—Cyst of *Toxoplasma gondii* in brain of sheep IV 37 weeks after inoculation. (×500.)

The other two sheep (IV and I) were kept until Dec. 2. Our object was to find how long sheep muscle may remain infective, and to make further observations on the dye-test titre in a sheep with a fairly long-continued infection. The experiments were more rigidly controlled by keeping the control animal (sheep I) also for as long as possible before parasitological examination.

Passage of brain and skeletal muscle from the control sheep failed to reveal toxoplasma, and the dye test remained negative. The dye test of sheep IV still showed a titre of 1/800, and toxoplasma was readily isolated from brain and skeletal muscle. A cyst (fig. 3) was seen in a section of its brain (i.e., at the 37th week of infection) which measured 70 $\mu \times 45$ μ, presumably having been distorted to an oval shape during growth. Inoculation of suspensions of diaphragm and heart-muscle caused no infection in the multimammate rat.

The heart and skeletal muscle of these two sheep (I and IV) was infected with *Sarcocystis tenella*. Cysts were fairly plentiful in the sections, some longitudinal (150 μ long), and others horizontal (35–40 μ diameter); they contained large spores, easily differentiated from toxoplasma. We kept the sheep under protected conditions, and they probably contracted sarcocystis as young lambs before coming to the laboratory. The skeletal muscle of sheep IV was thoroughly examined in biopsies taken during the 4th and 14th experimental weeks, and no sarcocysts were discovered. This suggests that *S. tenella* takes about 10 months to develop in muscle.

Discussion

We shall briefly summarise our findings before discussing their significance:

1. Four 15-week-old lambs, which had been given cysts of a sheep strain of toxoplasma by the intraperitoneal route (one), by the intravenous route (two), and by fine spray into the throat (one) all became infected. High dye-test titres appeared in those inoculated by intraperitoneal and intravenous routes within 2 weeks, but only between 2 and 4 weeks in the animal receiving parasites by throat spray. Within 4 weeks toxoplasma was readily isolated from muscle biopsy specimens from the first three sheep, and cysts were seen in muscle sections. The parasite could not be demonstrated directly in muscle from the sheep infected by inhalation. The same results were found when muscle was examined on the 79th day of infection. When three of these sheep were killed 16 weeks after inoculation, toxoplasma was isolated from the skeletal muscle and brain of all three animals, from heart-muscle in two, from liver in one, and from kidney in one. When the fourth sheep was killed 9 months after inoculation (intravenous), the skeletal muscle was still infected with toxoplasma, and the brain contained cysts. The dye-test titre of this sheep was still 1/800.

2. A sheep fed with large numbers of toxoplasma cysts did not become infected; a control lamb was also uninfected.

3. Cooking a leg of an infected sheep in a low-temperature oven for 40 minutes destroyed the parasites, even though much of the flesh in the centre of the joint remained completely raw.

4. Two of ten multimammate rats became infected after eating muscle from an infected sheep.

These findings show that sheep can harbour *T. gondii* for at least 9 months after infection, and that they remain in good health during this period, showing no macroscopic pathological changes. Although the organism persists in various edible parts of the carcass, their consumption is probably not hazardous for man because the organisms are killed by even the lightest of cooking.

It is just possible that repeated oral ingestion of dead toxoplasma in meat or other animal products might provoke antibody production as happens in some bacterial infections (Wilson and Miles 1955), and this might be responsible for the inexplicably wide distribution of cytoplasm-modifying antibodies in low titre in man. The actual danger to man of infected flesh is probably from the introduction of the parasite into wounds on the skin of butchers or other animal handlers (Beverley et al. 1954, Lainson 1958).

Conclusions

Five lambs became infected with a sheep strain of *Toxoplasma gondii* after being exposed by intravenous inoculations (two), by intraperitoneal inoculation (one), and by inhalation. Administration by mouth was unsuccessful. A control animal remained uninfected throughout the experiment.

The dye test became positive within 2 weeks, and it was still positive 9 months after infection.

The organism persisted in low density in the brain, skeletal and heart muscle, liver, and kidney.

Even gross undercooking of the meat killed the organism. Thus, in the ordinary way, eating infected meat does not constitute a hazard to man in this country.

We are grateful to Dr. C. Kulasiri of this laboratory for performing the earlier dye tests, and to Dr. D. G. Fleck of the Cardiff Public Health Laboratory Service for the later ones.

REFERENCES

Beverley, J. K. A., Beattie, C. P. (1952) *J. clin. Path.* **5**, 350.
— — Roseman, C. (1954) *J. Hyg., Camb.* **52**, 37.
— Watson, W. A. (1959) *Nature, Lond.* **184**, suppl. 26, 2041.
Cole, C. R., Sanger, V. L., Farrell, R. L., Kornder, J. D. (1954) *N. Amer. Vet.* **35**, 265.
Hartley, W. J., Marshall, S. C. (1957) *N.Z. vet. J.* **5**, 119.
Lainson, R. (1955) *Ann. trop. Med. Parasit.* **49**, 397.
— (1958) *Trans. R. Soc. trop. Med. Hyg.* **52**, 396.
Rawal, B. D. (1959) *Lancet*, **i**, 881.
de Roever-Bonnet, H. (1957) *Docum. Med. geogr. trop.* **9**, 17.
Wilson, J. S., Miles, A. A. (1955) *in* Topley and Wilson's Principles of Bacteriology and Immunology; vol. II, London.

MAGNESIUM METABOLISM IN INFANTILE PROTEIN MALNUTRITION

R. D. MONTGOMERY
M.A., M.B. Cantab., M.R.C.P.

MEDICAL RESEARCH COUNCIL TROPICAL METABOLISM RESEARCH UNIT, UNIVERSITY COLLEGE OF THE WEST INDIES, MONA, JAMAICA

IN spite of the high concentration of magnesium in human cells and its participation in many vital enzymic processes, very little is known about the effect of abnormal nutritional states on the magnesium content of tissues.

A constant relationship between potassium, phosphorus, and magnesium in human muscle was observed by Baldwin et al. (1952). In animals fed on specifically magnesium-deficient diets, a depletion of tissue-potassium has been demonstrated which correlates with, and may be relatively greater than, that of magnesium (Cotlove et al. 1951, MacIntyre and Davidsson 1958). It has been suggested that this drainage of potassium might be due to interference with the magnesium-dependent mitochondrial systems of energy production required for maintenance of normal potassium balance within the cell (Vitale et al. 1957, MacIntyre and Davidsson 1958). One practical implication is that failure to correct magnesium depletion might hinder the restoration of normal potassium metabolism.

Magnesium depletion in kwashiorkor has been suspected. Pille et al. (1958) reported in untreated cases a slight lowering of serum-magnesium, of doubtful significance. They found no consistent changes, however, in the magnesium concentration of morning specimens of urine during recovery.

Previous studies in this unit on muscle biopsy specimens from malnourished infants (Waterlow and Mendes 1957) revealed a tissue depletion of potassium and an excess of sodium even after initial treatment had restored the serum-electrolyte pattern to normal.

The technique of analysis has now been modified to include estimation of magnesium content by flame spectrophotometry. A gross tissue depletion of magnesium has been demonstrated, which closely parallels that of potassium. Urine studies during recovery show an avid magnesium retention prolonged over many weeks, in contrast to the relatively brief conservation of potassium and phosphorus. No corresponding changes were found in the magnesium content of serum or red cells.

Material

Serial studies were made on 27 infants aged 9 to 24 months suffering from kwashiorkor or the closely related clinical syndromes of protein malnutrition commonly observed in Jamaica (Jelliffe et al. 1954).

TABLE I—MAGNESIUM AND POTASSIUM CONTENT OF MUSCLE IN INFANTS WITH SEVERE PROTEIN MALNUTRITION (VALUES IN MEQ. PER KG. WET WEIGHT WITH STANDARD ERRORS OF MEANS)

First biopsy (12 cases)		Second biopsy (12 cases)		Fatal cases (10)	
Mg	K	Mg	K	Mg	K
10·1 ±0·56	56 ±3·56	13·9 ±0·87	70 ±4·19	12·0 ±0·75	66 ±6·48

Muscle biopsies were performed on 12 cases within 10 days of admission and were repeated 5 to 9 weeks later. Males were selected for cosmetic reasons. "Biopsies" by a similar technique were performed on 10 fatal cases within 15 minutes of death.

Methods

Fat-free samples of muscle weighing 50–150 mg. were taken under local anæsthetic from the pectoralis muscle in the anterior axillary fold. Specimens were weighed and wet-ashed for 48 hours in 0·2 *N* HNO_3. Electrolytes were estimated in the supernatant acid.

Magnesium estimations were made in a standard Unicam S.P. 900 flame spectrophotometer burning acetylene in air, against blanks containing appropriate dilutions of a "physiological" mixture of sodium, potassium, calcium, and phosphate.

No significant variation was found in the interference effects of these electrolytes on the magnesium emission at 285·2 mμ wavelength, over the ranges of concentration of them which were encountered in these specimens. Addition of known amounts of magnesium to the tissue extract gave recoveries of 102–104%.

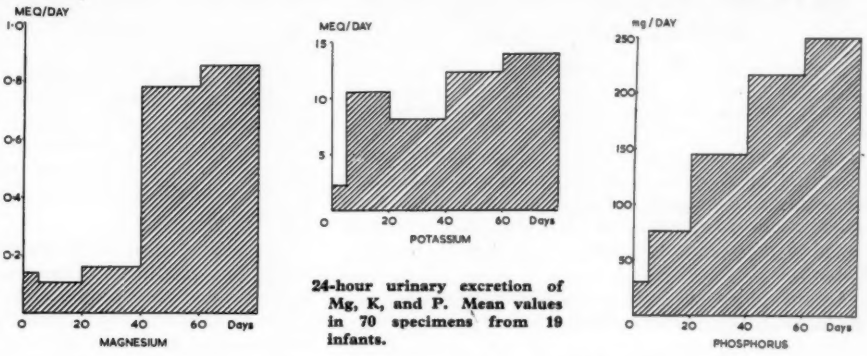
Serum was analysed in a dilution of 1 : 10, and washed red cells were lysed at a dilution of 1 : 25; again "physiological" blanks were used. Trapped plasma in the red-cell preparation was estimated from the protein content of washings (L. N. Went, unpublished data). Urine estimations were made on undiluted aliquots of acidified 24-hour or 48-hour collections.

TABLE II—MAGNESIUM CONTENT OF BLOOD IN 27 INFANTS RECOVERING FROM SEVERE PROTEIN MALNUTRITION (VALUES IN MEQ. PER LITRE WITH STANDARD ERRORS OF MEANS)

—	Days after admission		
	0–20	20–60	60+
Serum (40 specimens)	1·74 ±0·052	1·71 ±0·047	1·73 ±0·077
Red cells (60 specimens)	3·80 ±0·093	4·00 ±0·119	4·05 ±0·162

Results

The results of muscle and blood analyses are summarised in tables I and II, and normal figures for comparison are given in table III. The fatal cases showed a wider variation in muscle electrolyte state and are recorded separately. The concentrations in muscle are expressed in terms of wet weight. It was demonstrated previously (Waterlow and Mendes 1957) that changes in total water content of muscle in these infants before and after recovery were of the order of 2% and that electrolyte changes were equally valid when related either to wet weight or to non-collagen nitrogen.



24-hour urinary excretion of Mg, K, and P. Mean values in 70 specimens from 19 infants.

The accompanying figure shows the mean levels of 24-hour urinary excretion of magnesium at various stages of recovery compared to that of potassium and phosphorus.

Discussion

It has been shown that the potassium and magnesium concentrations in muscle of normal infants reach adult levels by the age of 4 months (Dickerson and Widdowson 1960). The mean values in the second biopsy specimens fell significantly below these levels; it is conceivable that the potassium content was influenced by inadequate magnesium repletion.

The urinary magnesium output represents the net difference between the amount absorbed and the amount retained in the body—in other words, the surplus of supply over demand. It therefore reflects the "magnesium status" of the individual, provided that there is no failure by the kidney to conserve magnesium.

TABLE III—SOME NORMAL VALUES FOR THE MAGNESIUM AND POTASSIUM CONTENTS OF MUSCLE AND BLOOD IN ADULTS (STANDARD DEVIATIONS IN ITALICS)

Tissue	Mg	K	Source
Muscle (mEq. per kg. wet weight)	17·3 (*0·96*)	89 (*14·6*)	Montgomery
	20·0 (Infants)	89·5 (Infants)	Dickerson and Widdowson (1960)
	16·3 (*2·48*)	91·3 (*8·32*)	Barnes et al. (1957)
	16·4 (*2·10*)	94·6 (*11·7*)	Baldwin et al. (1952)
Serum (mEq. per litre)	1·71 (*0·10*)	(West Indians)	Montgomery
	1·67 (*0·17*)	..	Van Fossan et al. (1959)
	1·83 (*0·27*)	..	Barker et al. (1959)
	1·72 (*0·16*)	(Bantu)	Bersohn and Oelofse (1958)
	1·65	(West African infants)	Pille et al. (1958)
	2·05 (*0·18*)	..	Wacker and Vallee (1957)
Red cells (mEq. per litre)	3·36	..	Fidler (1934)
	5·40 (*0·43*)	..	Greenberg et al. (1933)

The low urinary magnesium output in our cases probably results both from an increase in the amount retained, and from a decrease in the amount absorbed. Retention is likely to be increased as a result of the depletion shown by muscle analysis, and the rapid growth that occurs during recovery. The amount absorbed may be decreased both because of initial inadequate intake and because of malabsorption and diarrhœa. The daily intake in the early stages of treatment was 1–3 mEq., rising to 4–9 mEq. at the time of the second biopsy. We have as yet no information on the efficiency of magnesium absorption, but it seems likely that in the acute stages of protein malnutrition, when diarrhœa is usually present, significant amounts of magnesium as well as of potassium may be lost in the stools.

The results obtained on muscle and on urine, taken together, give evidence of magnesium depletion. The extent of this depletion in relation to total body magnesium is not known, since a large proportion of body magnesium is in the skeleton. In spite of this, blood levels of magnesium were normal. It therefore seems that, as with potassium, the 24-hour urinary output is a better index of depletion than the blood level.

The fact that urinary magnesium output was initially very low in spite of a normal serum-magnesium concentration suggests that renal conservation was well maintained. This is in keeping with the findings in experimental magnesium depletion (Fitzgerald and Fourman 1956, Barnes et al. 1958).

Increased tissue sodium and total body-water, often with sodium diuresis during recovery, are features of infantile protein malnutrition, with or without clinical œdema. It is of interest to note that similar changes were observed in man by Fitzgerald and Fourman (1956) in experimental magnesium deficiency and repletion—although their specificity is open to question.

No correlation was observed between the clinical state and the degree of magnesium depletion, and no symptoms could be directly attributed to it. The deficiency was no greater in the 10 fatal cases than in survivors. Preliminary observations in Mexico seem to confirm this finding (Metcoff 1959).

With the exception of studies by Wacker and Vallee (1957), MacIntyre and Davidsson (1958), and Van Fossan et al. (1959) all the other reports of magnesium estimations quoted in this paper have been based on chemical methods, which have repeatedly proved unsatisfactory in the experience of this unit. It is evident that reliable methods of flame spectrophotometry are now available.

I am grateful to Prof. J. C. Waterlow, director of this unit, who proposed and advised on this investigation, and also to Dr. L. N. Went, of the department of pathology of the University College of the West Indies, for much technical advice.

REFERENCES

Baldwin, D., Robinson, P. K., Zierler, K. L., Lilienthal, J. L. (1952) *J. clin. Invest.* **31**, 850.
Barker, E. S., Elkinton, J. R., Clark, J. K. (1959) *ibid.* **38**, 1733.
Barnes, B. A., Gordon, F. B., Cope, O. (1957) *ibid.* **36**, 1239.
— Cope, O., Harrison, T. (1958) *ibid.* **37**, 430.
Bersohn, I., Oelofse, P. J. (1957) *Lancet*, i, 1020.
Cotlove, E., Holliday, M. A., Schwartz, R., Wallace, W. M. (1951) *Amer. J. Physiol.* **167**, 665.
Dickerson, J. W. T., Widdowson, E. M. (1960) *Biochem. J.* **74**, 247.

References continued overleaf

GRAM-NEGATIVE BACTERIÆMIA WITH SUDDEN HYPOTENSION

R. T. ALDRIDGE
F.R.C.S.

SURGICAL REGISTRAR, UNIVERSITY COLLEGE HOSPITAL, LONDON, W.C.1; LATE SURGICAL REGISTRAR, BARNET GENERAL HOSPITAL

GRAM-NEGATIVE bacteriæmia is a potentially lethal complication of certain surgical procedures, particularly those involving the genitourinary tract. In published cases where such bacteriæmia has been associated with profound hypotension, the fatality-rate approaches 60% (table I).

In the following cases there was hypotension of a characteristic type which responded to treatment.

Case-reports

Case 1.—A 59-year-old labourer was admitted to Barnet General Hospital on July 12, 1959, with acute retention due to a large adenomatous prostate. Five days later a suprapubic transvesical prostatectomy was performed, the bladder being closed and drained by a urethral catheter. When the catheter was removed on the sixth postoperative day he passed urine normally and was allowed out of bed; but on the afternoon of the seventh day his general condition deteriorated suddenly and in ten minutes he was gravely ill. Details are given in table II.

TABLE I—SOME RECORDED SERIES

Author	No. of cases	No. with hypotension	Deaths	Comments
Jacob (1909)	39	..	16	..
Felty and Keefer (1924)	25	..	8	19 postoperative
Scott (1929)	82	..	11	Routine cultures on urological patients
Waisbren (1951)	29	15	5	19 followed operation or catheterisation
Wise et al. (1952)	53	8	6	..
Spittel et al. (1956)	137	7	30	68 postoperative (21 perurethral resection; 18 cystoscopy)
Reid (1957)	11	11	6	All with flush and gross hypotension
Slade (1958)	7	3	3	Urological

Case 2.—A sales manager, aged 51, had a twenty-five-year history of gonorrhœal posterior urethral stricture which had been dilated uneventfully on numerous occasions. Last July routine dilatation was followed by three days' pyrexia with malaise and rigors. When he came again in October, dilatation was unexpectedly difficult and accompanied by pain and bleeding. While resting in the recovery room he complained of "jumping" in the lumbar region and had a rigor. His systolic blood-pressure was found to be 50 mm. Hg but in ten minutes was unrecordable. Within half an hour of his dilatation he had become gravely ill (table II).

In case 1 the provisional diagnosis of bacteriæmia was made only after general examination and electrocardiography had suggested that the sudden hypotension was not of cardiac or pulmonary origin. In case 2, presenting with similar sudden hypotension, fluid bowel motions, and flushing of the extremities, the diagnosis was made immediately.

In both cases the organism was obtained in heavy pure culture from the blood after twenty-four hours' incubation, but in neither was it obtained in pure culture from the urine. Nevertheless it probably originated in the urinary tract. (Case 1 had otitis media of fifteen years' standing, but the swab yielded *Proteus vulgaris*, not the *Pr. morgani* found in the blood.)

Discussion

The two case-histories are remarkably similar in that both patients became suddenly ill with hypotension, pyrexia, and tachycardia, passed fluid stools, and had a flushed appearance with warm dry extremities rather than the expected pallor with cold clammy limbs. Although they fell asleep frequently, they would wake at the slightest

TABLE II—THE TWO CASES

—	Case 1	Case 2
Condition	Prostatic adenoma Acute retention	Posterior urethral stricture
Time of collapse after operation	Seven days	Thirty minutes
Lowest systolic blood-pressure	40 mm. Hg	Unrecordable
Highest pulse-rate	164 per min.	120 per min.
Highest temperature	105°F	102·6°F
Temperature normal in	Twelve hours	Twelve hours
Colour when hypotensive	Very flushed	Flushed with blue tinge
Extremities	Warm and dry	Warm and dry
Mental state	Drowsy but alert and cooperative when roused	
Fluid bowel motions	Four in first two hours	Five in first hour
Blood-culture	*Proteus morgani*	*Escherichia coli*
Antibiotic sensitivities	Resistant to all drugs in vitro	Sensitive only to chloramphenicol
Urine culture (on admission)	*Esch. coli; Pr. morgani*	Mixed culture, probably contaminants
White-cell count (per c.mm.)—		
Originally	35,000 (95% polymorphs)	36,900 (93% polymorphs)
Sixth day	16,000	15,000
Hæmoglobin—		
Originally	102%	92%
Sixth day	73%	75%
Blood-urea (per 100 ml)—		
Originally	36 mg.	60 mg.
Fourth day	58 mg.	79 mg.
Specific gravity of urine on fifth day	1012	1012
17-Ketosteroid estimation (24 hours)—		
Fourth day	3·5 mg.	2·5 mg.
Recovery	8·2 mg.	11·0 mg.
Serum-bilirubin (per 100 ml.)—		
Fourth day	5·0 mg.	2·2 mg.
Tenth day	0·8 mg.	0·6 mg.
Treatment	Chloramphenicol Hydrocortisone *l*-Noradrenaline	Chloramphenicol Hydrocortisone *l*-Noradrenaline
l-Noradrenaline period	Seventy-two hours	Seventy hours
l-Noradrenaline total dose	48 mg.	54 mg.
Complications	Suprapubic fistula Calf-vein thrombosis Pulmonary atelectasis Epididymitis	Hæmoptysis (? origin) Calf-vein thrombosis Purulent bronchitis

DR. MONTGOMERY: REFERENCES—*continued*

Fidler, A. (1934) *Bull. internat. Acad. Polon* (cl. med.) p. 13.
Fitzgerald, M. G., Fourman, P. (1956) *Clin. Sci.* **15**, 635.
Greenberg, D. M., Lucia, S. P., Mackey, M. A., Tufts, E. V. (1933) *J. biol. Chem.* **100**, 139.
Jelliffe, D. B., Bras, G., Stuart, K. L. (1954) *W.I. med. J.* **3**, 43.
MacIntyre, I., Davidsson, D. (1958) *Biochem. J.* **70**, 456.
Metcoff, J. (1959) Personal communication.
Pille, G., Palancade, P., Lunven, J. (1958) *Bull. med. A.O.F.* **3**, 41.
Van Fossan, D. D., Baird, E. E., Jekell, G. S. (1959) *Amer. J. clin. Path.* **31**, 368.
Vitale, J. J., Nakamura, M., Hegsted, D. M. (1957) *J. biol. Chem.* **228**, 573.
Wacker, W. E. C., Vallee, B. L. (1957) *New Engl. J. Med.* **257**, 1254.
Waterlow, J. C., Mendes, C. B. (1957) *Nature, Lond.* **180**, 1361.

touch and were then fully conscious, alert, and cooperative. Pain was not a feature of the illness.

The rapid resolution of the pyrexia may suggest either transient bacteriæmia or a rapid response to the antibiotic given. Both suggestions are belied by the long-continued polymorphonuclear leucocytosis, and a more acceptable explanation may be the non-specific action of steroids in an allergic phenomenon.

Two days' oliguria was followed by a mild diuresis with fixed specific gravity, and the blood-urea rose as shown, suggesting some transient renal damage. The figures for 17-ketosteroids in the urine might imply adrenal hypofunction returning slowly to normal, but are invalidated by the coincident steroid therapy.

The cause of the hypotension is problematical. The fact that gram-negative organisms are circulating in the blood does not necessarily mean that the patient will be shocked. Spittel et al. (1956) found 137 cases of such bacteriæmia, of which only 7 were collapsed. Wise et al. (1952) cite 53 cases with only 8 in shock.

The object of treatment is twofold—to attack the bacteria with antibiotics and to maintain life until the infection is overcome. In these cases the antibiotic chosen was chloramphenicol and it was given for eight days—at first intravenously (1·0 g. six-hourly) but later by intramuscular injection and finally by mouth. The blood-pressure was maintained by intravenous infusion of *l*-noradrenaline. Hydrocortisone hemisuccinate (100 mg. six-hourly) was given intravenously for the first two days and followed by diminishing oral doses of prednisone for four weeks.

Many urologists will remember patients dying shortly after urethral dilatation or cystoscopy with hypotension and a high colour. Necropsy in these cases usually shows some hæmorrhages in solid organs but no conclusive evidence of the cause of death.

Reid (1957) suggests, among other possibilities, a Shwartzman phenomenon. This requires a preparing dose of foreign protein, which may be bacterial in origin, followed by a provoking dose of the same or allied substance after an interval of at least twenty-four hours. Case 2 fits perfectly into this scheme: at the July dilatation he had his preparing dose, and this was followed by the provoking dose at the dilatation in October. In case 1 it is possible that the patient had a preparing dose at the time of operation (for his temperature rose to 104°F postoperatively and settled quickly), and that a further small dose on the seventh day provoked a Schwartzman phenomenon. If the shock is indeed anaphylactic, anti-histamine drugs could be useful.

It is generally agreed that an effective antibiotic must be given early and in sufficient dosage, but the possibility that bactericidal drugs may release more toxin and increase shock should be kept in mind.

My thanks are due to Mr. Alan Small (case 1) and Mr. V. J. Downie (case 2), under whose care the patients were admitted, both for permission to make this report and for their help in its preparation.

REFERENCES

Felty, A. R., Keefer, C. S. (1924) *J. Amer. med. Ass.* **82**,1430.
Jacob, L. (1909) *Dtsch. Arch. klin. Med.* **97**,303.
Reid, J. D. (1957) *N.Z. med. J.* **56**, 200.
Scott, W. W. (1929) *J. Urol.* **21**, 527.
Slade, N. (1958) *Proc. R. Soc. Med.* **51**, 331.
Spittel, J. A., Martin, W. J., Nichols, D. R. (1956) *Ann. intern. Med.* **44**, 302.
Waisbren, B. A. (1951) *Arch. intern. Med.* **88**, 467.
Wise, R. I., Shaffer, J. M., Spink, W. W. (1952) *J. Lab. clin. Med.* **40**, 961.

Preliminary Communication

AUTOLOGOUS GLIOMA TRANSPLANTATION

MUCH knowledge of the biological characteristics of gliomas has been gained in recent years from animal experiments. Zimmerman [1] used various coal-tar derivatives to induce glioma formation in the brains of mice, and he perpetuated these growths as homologous subcutaneous implants. Perese and Moore [2] described techniques by which such implants can be used to test the efficacy of various therapeutic approaches—e.g., chemotherapy or radiation. Since glioma transplants showed no tendency to metastasise in animals, we thought that human autologous transplantation would be safe. The relative hopelessness of the more malignant gliomas in man seemed to justify investigations that might add to our knowledge of their behaviour.

In August, 1957, one of us (W. H. B.), working at the Manhattan Veterans Hospital, participated in a study on a patient undergoing craniotomy for a recurrent right frontal malignant glioma. After fully explaining the nature of the procedure to the patient, small pieces of the tumour were implanted into the subcutaneous tissues of his thighs. Within 3 months tumour had grown at several implantation sites. The patient survived $11\frac{1}{2}$ months after the implantation, and his general condition was good for most of this period. Biopsies showed the implants to be histologically similar to the primary brain tumour. This case was mentioned at the April, 1959, meeting of the Harvey Cushing Society, with the suggestion that further similar studies should be performed.

Zimmerman [3] reports that in his animal studies some homologous subcutaneous transplants regressed after a time. When this had happened no more "takes" could be obtained with the same tumour tissue, although other tumours could be transplanted successfully in the same animal. This was attributed to antibody formation. Three questions came to mind regarding further studies in man: (1) will antibodies be formed in response to human autologous implants? (2) If so, can such antibody production be further enhanced? (3) Will anti-tumour antibodies influence the growth of the primary tumour?

In a preliminary study at the neurosurgical unit of St. George's Hospital, from October to December, 1959, five patients with malignant gliomas underwent autologous implantation at the time of craniotomy. In each case the procedure was explained and permission obtained after a burr-hole biopsy had established the diagnosis. Minced tumour tissue was injected subcutaneously through a no. 15 gauge needle at twelve sites. Two patients died of their intracranial lesion within 2 months, before they could be followed up, and two of the remaining cases have developed significant lesions at the site of implantation. Studies have been completed in one of these, which is reported here.

Case-report

A man, aged 37, was admitted to St. George's Hospital under the care of one of us (W. McK.) on Nov. 25, 1959, with a 2-week history of right-sided headache, anorexia, and transient weakness of the left leg. The left eye was missing as a result

1. Zimmerman, H. M., *Amer. J. Path.* 1955, **31**, 1.
2. Perese, D. M., Moore, G. E. Report to the Harvey Cushing Society, April, 1959.
3. Personal communication.

of old trauma, and he had early papillœdema of the right fundus. No other neurological signs were found. Lumbar puncture yielded clear cerebrospinal fluid under a pressure of 280 mm. water, with a protein level of 80 mg. per 100 ml. Plain radiographs were normal. Ventriculography, performed through posterior-parietal burr-holes, showed displacement of the lateral and third ventricles to the left and elevation of the right temporal horn. A biopsy specimen of the tumour mass in the right temporal lobe was obtained through a burr-hole over the lesion. Histologically this was an astrocytoma, malignancy grade III, according to Kernohan's [4] classification. A right temporal craniotomy was then performed, and a large quantity of tumour tissue was removed. A total of 15 ml. of this material was injected directly into the subcutaneous tissues of the thighs at twelve injection sites. The post-operative course was uneventful, and the patient was discharged home on Dec. 7.

On March 29, 1960, he was readmitted to the hospital with headache and vomiting. He was mentally slow and had increasing papillœdema. Tumour had grown in ten of the twelve implants. Most of these can be seen in fig. 1. They were soft, rather like lipomas in consistence, and the two largest lesions had reached a maximum diameter of 8 cm. In biopsy specimens, the tumours appeared macroscopically to be encapsulated. Histological examination revealed a tumour consisting of pleomorphic cells, many bipolar and some multipolar, associated with occasional astrocytic fibres (staining blue with phosphotungstic-acid/hæmatoxylin); there were large regions of necrosis and occasional mitotic figures were present. The appearance was that of an astrocytoma, malignancy grade III, as in the original cranial biopsy.

Both tumours contained considerable reticulin; but this was not intimately related to tumour cells, nor was it arranged as in sarcomatous change of the vascular endothelium. The appearance in the cranial biopsy suggested invasion of the leptomeninges (shown at subsequent necropsy to be widespread) and in the transplant invasion and incorporation of the subcutaneous mesoderm. Fig. 2 shows the similarity of the two tumours.

Immunological studies by the tanned-red-cell, double diffusion in agar gel, immuno-electrophoretic, and complement-fixation techniques were carried out, and no evidence of an antibody-antigen system was found.

The patient's condition deteriorated rapidly, and he died on April 6. Necropsy revealed much swelling of the posterior part of the right cerebral hemisphere, which was occupied by a 5 cm.-wide necrotic and hæmorrhagic tumour, with bilateral uncal herniation. Tumour was infiltrating the tentorium of the cerebellum, the leptomeninges of the brain-stem, and the 5th, 7th, and 8th cranial nerves bilaterally. The inguinal lymph-glands on both sides were carefully examined. Although macroscopically there was no evidence of involvement by tumour, three lymph-glands on the left side were found on histological examination to contain apparently actively growing glioma of the same nature as that of the transplants and the primary. Sections of the remaining transplants showed no true capsule formation. The remaining organs were not significantly abnormal.

4. Kernohan, J. W., Mabon, R. F., Svien, H. J., Adson, A. W. *Proc. Mayo Clin.* 1949, **24**, 71.

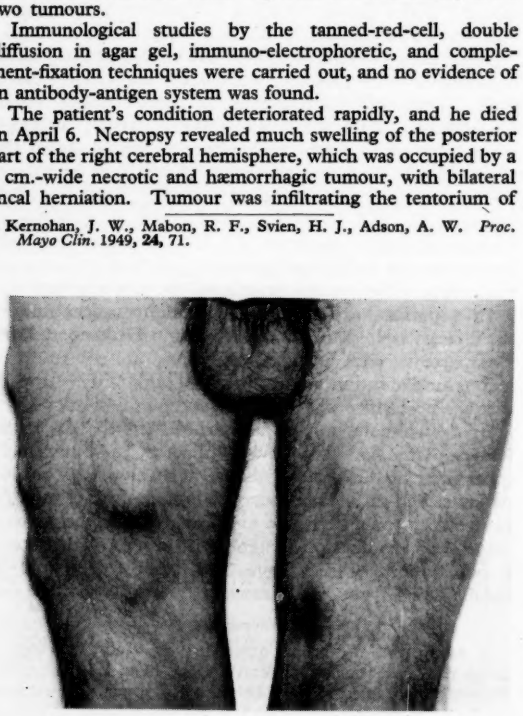


Fig. 1—Appearance of implanted gliomas.

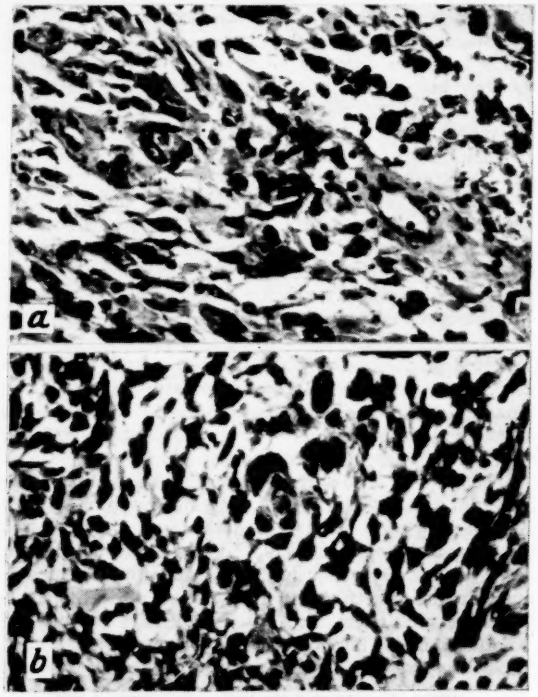


Fig. 2—Gliomas: *a*, cerebral; *b*, implanted. (×175.)

Further studies are in progress at St. George's Hospital on this and other cases. Similar work is being conducted by Dr. Dogan Perese at the Roswell Park Memorial Institute in Buffalo, New York.

We wish to thank Prof. T. Crawford for encouragement and advice, and Mr. G. Franglen, B.SC., for carrying out the immuno-electrophoretic studies.

Department of Neurosurgery, WILLIAM H. BLOOM M.D.
Department of Pathology, KELVIN C. CARSTAIRS M.B. Lond.
Departments of Neurosurgery and Pathology, Department of Neurosurgery, St. George's Hospital, London, S.W.1 M. R. CROMPTON M.B. Lond.; WYLIE MCKISSOCK O.B.E., M.S. Lond., F.R.C.S.

"A national policy which set out to increase opportunities for training in social work would in itself be a recognition of the professional nature of the service provided by social workers. The lesson would not be lost on the laymen in the local authorities and voluntary organisations responsible for making appointments. The increased opportunities for training and acquiring a professional qualification would remove much of the frustration and insecurity which is at the back of much of the muddled thinking and unprofessional behaviour of not a few social workers."—*Portrait of Social Work.* BARBARA N. ROGERS and JULIA DIXON. London, 1960.

Reviews of Books

Pædiatric Pathology

DANIEL STOWENS, M.D., pathologist, Children's Hospital Society of Los Angeles, and associate professor of pathology, University of Southern California. Baltimore: Williams & Wilkins. London: Baillière, Tindall, & Cox. 1959. Pp. 676. 160*s*.

THE writing of a comprehensive account of pathology to satisfy the requirements of both pathologists and pædiatricians is a task which has long been neglected by pædiatric pathologists. It is not sufficient for the author to have a wide experience of cases that he has himself investigated; his experience must also be enhanced by long contact with clinical pædiatrics. He must be conversant too with adult pathology, embryology, and physiology, have an extensive knowledge of the literature, and be capable of assessing the divergent theories which abound in many pædiatric problems.

This first book on the subject is a valiant attempt to present a complete picture of pædiatric pathology and is comparatively free of omissions and errors. It suffers, however, from a general lack of uniformity between its various sections. The first half, dealing mainly with disease from an ætiological standpoint, is expanded by the inclusion of much superfluous clinical detail together with elementary epidemiology, bacteriology, and pathology of a standard inconsistent with the subject; the second half, in which diseases are classified anatomically, tends to be deficient in clinical correlations. Large sections which are adequately dealt with in standard works in pathology could be considerably curtailed. Several relatively common conditions are sketchily described, some rare diseases receive lengthy treatment, and a few diseases which have never been reported in children are included.

The emphasis throughout is on histology. Gross appearances are regarded as obvious, and almost all of over 450 illustrations are photomicrographs; the failure to appreciate disease processes from the gross findings at necropsy may lead a pathologist into serious error, especially in those cases requiring histochemical or virological investigation. A rather superficial account of congenital heart-disease is rendered virtually useless, and sections on embryology became less intelligible, because gross photographs and diagrams are omitted. The quality and didactic merit of the illustrations deserve the highest praise, but the captions are not always adequate.

Instead of treating subjects in an orderly manner, ending with theoretical and problematical matters, discussions and hypotheses are often mixed with facts. Dissertations are generally to the point, although it is a pity that the author has not analysed the large number of cases at his disposal to back up his theories. No references are given in the text to a bibliography which is mostly well chosen and up to date.

Although the technique of examining the infant head is described, little is said about the external appearance or the examination of the organs. Details of necropsy technique on the newborn would be of such value to most pathologists that a separate appendix seems justified.

In spite of these criticisms, there is a great deal of value in Dr. Stowens' book. Pathologists faced with pædiatric problems will almost certainly be helped by reference to its pages, and pædiatricians will gain a deeper knowledge of basic pathological processes than is to be found in textbooks of pædiatrics. Since it bridges the gap between textbooks of neonatal and adult pathology, it must join Morison, Potter, and Willis on the shelves of all pædiatric and pathological libraries.

The Roots of Crime

Selected Papers on Psychoanalysis. Vol. II. EDWARD GLOVER, M.D., LL.D. London: Imago. Pp. 422. 45*s*.

ALTHOUGH there is little new in this collection of Dr. Glover's contributions on delinquency, it is valuable to have them in one volume. The ætiology, diagnosis, and treatment of pathological delinquency, criminal psychopathy, sexual perversions, and prostitution are discussed from a psychoanalytic viewpoint, and the broader issues of the McNaughten rules and prevention of crime get critical examination. Accurate diagnosis (unfortunately not yet possible) is regarded as the prerequisite of rational criminology, but Dr. Glover is scathing about factorial examination of descriptive criteria as being responsible for "the bastard concept of the continuum"; and he criticises the two antithetical analytic tendencies to apply the same unconscious formula to all cases, or to vary widely the emphasis laid on ætiological factors according to the theoretical predilections of the observer. The main place of psychoanalysis is seen as in research rather than therapy, and the application of analytic ideas in a broader setting is regarded favourably (Aichorn gets particularly enthusiastic praise). His condemnation of "half-boiled social workers, half-trained in analytic techniques" somewhat surprisingly places him on common ground with Lady Wootton.[1] The clichés of "broken home" and "separation anxiety" also come in for some rather harsh criticism.

Dr. Glover presents his forthright views in a lucid and stimulating way (though sometimes he is a little one-sided) and there is much of interest here for all concerned about crime and delinquency. It is unfortunate that the title should be identical with one already used by Sir Norwood East.[2]

Asklepios

Archetypal Image of the Physician's Existence. C. KERÉNYI. London: Thames & Hudson. 1960. Pp. 151. 30*s*.

Professor Kerényi, formerly professor of classics and the history of ancient religion in the universities of Szeged and Pécs, now living in Switzerland, invites the reader to accompany him on a tour of the sites where the cult of Asklepios, god of medicine and god of Greek physicians, was practised (the Romans called him Aesculapius). The chief places were Epidauros, Athens, Cos, and Pergamon in Asia Minor, and in all there are extensive remains of the sanctuary of the god. The patient went there to meet the god half-way, and the visit was often accompanied by visions. In many of these dreams the god intervened directly, and case-notes have been recorded. Pamphaes of Epidauros was afflicted with a "festering abscess of the mouth. Sleeping in the innermost chamber of the sanctuary, this man beheld a vision: he dreamed that the god opened his mouth, held his jaws apart with a wedge, and cleansed the mouth. Thereupon he became well." Dying and pregnant patients were not admitted. The priests were certainly not without medical training or ability; but their role, aside from deciding whom to admit, seems to have been largely passive. Barren women came to Epidauros to be impregnated by the god. "Nikesibule of Messene," says one of the records, "slept in the sanctuary in order to be favoured with progeny and beheld a dream. She dreamed that the god had come to her, followed by a snake with which she copulated. And within a year she gave birth to two boys."

This beautifully illustrated book will greatly interest classical scholars, and any doctors about to visit the four places it describes.

Introduction to Pharmacology

J. J. LEWIS, M.SC., senior lecturer in experimental pharmacology, University of Glasgow. Edinburgh: E. & S. Livingstone. 1960. Pp. 826. 55*s*.

THERE is need in this country to bridge the gap between the pharmacologist and the doctor, and Mr. Lewis' book is certainly a step in the right direction. It is not a textbook of therapeutics; but it presents the elements of pharmacology, as far as is possible, in an orderly and scientific fashion. The style is clear if rather pedestrian, and enables those unfamiliar with the jargon of pharmacologists to understand not only the effects of a drug but something of its mode of action as well.

Mr. Lewis' general approach is that of orthodox contemporary pharmacology, and he pays considerable attention to the relation between the chemical structure of drugs and their

1. Wootton, B. Social Science and Social Pathology. London, 1959.
2. The Roots of Crime (edited by Sir Norwood East). London, 1954.

effects where logical pictures of drug action are being attempted. The book should be useful to preclinical students as a supplement to some of the smaller textbooks. It could also be read with benefit by clinical students and by anybody who uses drugs and wishes to understand more clearly the nature of their action.

Hämatologischer Atlas

HORST STOBBE, DR. MED., Oberarzt, 1st Medical University Clinic, Charité Hospital, Berlin. Berlin: Akademie. 1959. Pp. 304. 119*s*.

THE heart of this book is the collection of 233 coloured illustrations of normal and abnormal blood and bone-marrow cells. These are all reproductions from direct colour photographs, and it is fair to say that no better illustrations have appeared anywhere. The magnification used is 2000 times, and this large scale has been accomplished while maintaining a notable clarity of detail; even the early megaloblasts are recognisable and this is a test that many current atlases fail to meet. The colours are good and contrast everywhere excellent. The publishers have taken great care with the reproductions and not one of the figures shows any blurring caused by printing faults. Every normal type of cell and a comprehensive selection of pathological cells is illustrated by photographs of single cells, groups of similar cells, or sometimes small groups of different cells.

In addition to the colour photographs there are 160 black-and-white pictures of cells taken by phase-contrast techniques. These are also very well reproduced but are of less interest. About half the book is text: opposite each page of illustrations there are brief descriptive legends, but most of the text is taken up by detailed morphological descriptions of the various types of cells and their importance and significance in diseases of the blood-forming tissues. This part of the book is undistinguished. There are 34 pages about techniques, a relatively short bibliography, and indices. The arrangement of the book makes it useful for reference, but hard to use as an aid to diagnosis. If you want to know what a megakaryoblast looks like, fig. 151 will show you; if you wonder what is the odd cell you are looking at, you will have difficulty in finding out from this book even if you can place the type of cell to which it belongs. It is a pity that Dr. Stobbe did not content himself with a true atlas—just the colour photographs and the minimum of description. The text and the phase-contrast pictures add greatly to the bulk of the book with little corresponding benefit. There are in print one or two atlases in English of equal standard to this one, but Dr. Stobbe's illustrations should make the authors and publishers of most English and American hæmatological books resolve to do better, or leave coloured illustrations out.

Lecture Notes on Ophthalmology

PATRICK D. TREVOR-ROPER, M.D., F.R.C.S., assistant ophthalmic surgeon, Westminster Hospital, and chief clinical assistant, Moorfields Eye Hospital, London. Oxford: Blackwell Scientific Publications. 1960. Pp. 94. 12*s*. 6*d*.

THIS brief selection of lecture notes presents a coup-d'œil of some of the more important ocular lesions, and is intended for the final-year student. Its illustrations are numerous, and since inspection forms so important a part of ocular diagnosis much may be learnt from them. Dogmatism is inevitable and welcome in a work of this type; but the devotion of space to operative details further compresses the references to diagnosis and ætiology which are much more important to the student at this stage.

Essentials of Orthopædics (3rd ed. London: J. & A. Churchill. 1959. Pp. 576. 70*s*.).—Just over ten years have elapsed since Mr. Philip Wiles' book first appeared. The extensive revisions that he has made in this edition are in themselves an interesting commentary on orthopædic progress over the past decade. Arthroplasty is now less prominent in the chapter on the treatment of osteoarthritis of the hip, and its place is taken by displacement osteotomy (though there is a paragraph dealing with the difficult legacies that the earlier vogue has left for many surgeons). Laminectomy is less often to be invoked in the management of sciatica, and two years in hospital is no longer almost mandatory for the child with Perthes' disease. In treating congenital dislocation of the hip the popularity of manipulative reduction has continued to wane. One condition—tuberculous arthritis—is now seldom seen in this country, and the very complete revision of the section devoted to it is necessary because this book is widely used abroad. These and many other amendments have almost completely changed the original text. Some very important aspects of the work are, however, unaltered. Its compactness and readability and Mr. Wiles' clear style are features which will ensure a continued demand for his book.

New Inventions

ADAPTORS FOR PÆDIATRIC ANÆSTHESIA AND RESUSCITATION

THE endotracheal connectors shown in fig. 1 have been designed for anæsthesia and resuscitation of neonates and small children. Four sizes are made (A, B, C, and D). The vertical piece allows small endotracheal tubes to be threaded on to the connector with an even distension of the tube; and thus splitting of the tube, which may occur when a tapered corrugated vertical piece is used, is avoided. Size A is made to take the smallest size of armoured latex tube. The vertical piece has the maximum possible inner lumen, to reduce resistance to respiration.

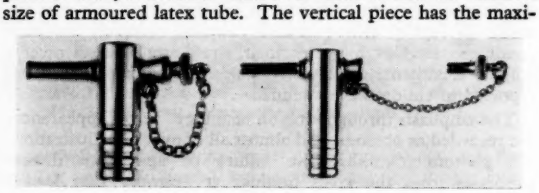


Fig. 1.

Fig. 2.

Fig. 3.

The suction union with the stopper removed will convert the connector so that it may be used as an Ayres T-piece and a rubber tube may be attached to it.

The fitting shown in fig. 2 is as an adaptor to attach to a small facepiece with the standard gas-inlet orifice (fig. 3). The upper part of the adaptor fits the rubber tubing of the patient's end of Ayres T-piece (or its modifications incorporating a reservoir bag).

This adaptor allows inhalational induction of anæsthesia or oxygenation to precede endotracheal intubation without alteration of the basic apparatus, and it is so made as to minimise dead space. The changeover is facilitated by disconnecting the adaptor and inserting the rubber tubing of the patient's end of the Ayres T-piece on to the horizontal end of the endotracheal connector.

The endotracheal connectors and the facepiece cap adaptor are obtainable from Messrs. A. Charles King, Ltd., 27, Devonshire Street, London, W.1, to whom thanks are due for help in producing the prototypes.

JACK LEVIN
M.B., B.SC. Cape Town, F.F.A. R.C.S.

Cape Town

THE LANCET

LONDON 9 JULY 1960

Leukæmia

THE increasing intensity of research into leukæmia is reflected in the May issue of the *American Journal of Medicine*, which is largely devoted to a symposium on leukæmia introduced by Dr. JOHN S. LAWRENCE [1] of Los Angeles. He points out that "definite advances have been made in our attack on it during the past quarter of a century but we are still far from any definitive answer to the problems presented by it". Ætiology remains mostly obscure, but there is no longer any doubt about the leukæmogenic effect of radiation. The development of drugs that have proved valuable in treatment has led to studies on the basic abnormalities. One of the most useful biochemical discoveries is the reduction in alkaline phosphatase in the granulocytes of chronic myeloid leukæmia. Electron microscopy has opened large new fields, "but whether this will result in the discovery of a means for eradicating the disease can well be doubted". Investigations on the dynamics of white blood-cells have produced some facts that will make us change our ideas. LAWRENCE cites the discovery that the turnover of desoxyribosenucleic acid in a collection of white cells composed mostly of blast cells is very slow; this suggests that the cells are not dividing rapidly but more slowly, so that the great increase of cells is due to accumulation and failure of maturation.

CRONKITE et al.[2] analyse the data about radiation and leukæmia, and present a succinct account of the evidence so far reported. Some 226 cases have been published—123 among survivors from the atom-bomb exposure in Japan, 55 among patients who had received deep X-ray therapy for spondylitis, and 9 among patients who had received radioactive iodine for hyperthyroidism. On the question of leukæmia induced in infants by exposure of the mother to diagnostic X-rays for pelvimetry, they declare that later evidence does not support STEWART et al.[3]; the choice of controls can apparently influence the results significantly,[4] and it is important to have further evidence to settle this question. CRONKITE et al. consider that there is enough evidence to state that exposure to doses of 100r or over carries a definite risk of leukæmia: "approximately 1 to $2/10^6$ persons at risk/year/rad, at least from approximately the second to the fifteenth year following exposure". They do not think that there are enough data to predict the risk of doses below 100r or indeed for stating whether there is any risk; they also hold that the evidence is insufficient for deciding whether or not there is a threshold dose for the induction of leukæmia or whether localised accumulations of a radioactive material such as strontium-90 can induce leukæmia.

SYVERTON and ROSS [5] discuss the theory of the ætiology of leukæmia—a subject which has been debated since 1908.[6] Investigations have been restricted almost entirely to birds and rodents, and SYVERTON and ROSS doubt how far the results are applicable to the disease in man. But this work does indicate the lines of research that are likely to prove best in man: it will be necessary to isolate and titrate these viruses, to show proliferative action, and to establish their human origin. These workers point out, too, that "induction of neoplastic effect by leukemogenic virus must depend on infections as opposed to genetic transmission if virological control is to be practicable", and they remind us that in virus-induced neoplasia infection precedes disease by a considerable time. SYVERTON and ROSS believe that tissue-culture techniques provide the best hope of testing the virus theory in man, but add that epidemiological methods such as those suggested by BURNET [7] may have a place.

Changes in the metabolism of leukæmic leucocytes are dealt with by VALENTINE.[8] Differences between normal and leukæmic cells are most obvious in alkaline phosphatase activity and in glycolysis and respiration. Leukæmic granulocytes are deficient in alkaline phosphatase; and in chronic leukæmia cells utilise less glucose, consume less oxygen, and produce less lactic acid than normal cells. CRADDOCK [9] reviews the very interesting work on the survival and life-span of the granulocyte series of cells, including myeloblasts. The average life-span of a polymorph granulocyte in the blood is about one day, but there is evidence that five or six days are spent in a marrow "pool" before release. In normal marrow cells divide or mature; whether they remain at one stage or not they will die, and the turnover is rapid. But in leukæmic marrow cell survival has been found to be prolonged and mitosis takes place *less* frequently than normal. The consequence is that proliferation outstrips even accelerated destruction of cells and the population of the marrow becomes increasingly immature. Eventually most of the cells in the marrow are stem or blast cells capable of infinite division as long as they can stay alive.

The metabolic changes in leukæmic cells should influence the development of drugs for the control of leukæmia. This subject is dealt with in a thoughtful

1. Lawrence, J. S. *Amer. J. Med.* 1960, **28**, 671.
2. Cronkite, E. P., Moloney, W., Bond, V. P. *ibid.* p. 673.
3. Stewart, A., Webb, J., Giles, D., Hewitt, D. *Lancet*, 1956, ii, 447.
4. Simpson, C. L., Hempelmann, L. H. *Cancer*, 1957, **10**, 42.
5. Syverton, J. T., Ross, J. D. *Amer. J. Med.* 1960, **28**, 683.
6. *Lancet*, 1958, ii, 30.
7. Burnet, F. M. *New Engl. J. Med.* 1958, **259**, 423.
8. Valentine, W. N. *Amer. J. Med.* 1960, **28**, 699.
9. Craddock, C. G., Jr. *ibid.* p. 711.

article by KRAKOFF.[10] Successful treatment may depend on the drug's ability to influence a metabolic pathway which is vulnerable in a particular type of leukæmia and even in a particular case. The various drugs now used for the control of leukæmia illustrate these differences. The anti-metabolites, such as amethopterin, which is a folic-acid antagonist, and 6-mercaptopurine, which influences an earlier stage in nucleic-acid synthesis (possibly the incorporation of hypoxanthine into nucleic-acid purines), are effective in acute blast-cell leukæmias, and 6-mercaptopurine is effective in chronic myeloid leukæmia; but this group of substances has no action in chronic lymphatic leukæmia. KRAKOFF suggests that the difference may be in the ability of lymphocytes to utilise "large polynucleotide fragments for nucleic acid synthesis"—a metabolic pathway not blocked by these drugs. The alkylating agents—nitrogen mustard and its variants—act by denaturing or inactivating desoxyribose-nucleic acid; they can reduce a raised white-cell count in both chronic and acute leukæmias; but whereas in chronic leukæmia such treatment is accompanied by a rise in red cells and hæmoglobin and by general clinical improvement, in acute leukæmia these changes do not occur. In acute leukæmias destruction or suppression of abnormal cells is not enough to produce a remission. In addition there must be replacement of abnormal cells in marrow and blood by normal cells; and so far corticosteroids have proved most useful in effecting this replacement. Consequently the combination of steroid with an anti-metabolite or an alkylating drug is at present the approved treatment for acute leukæmia. The pharmacological chemists have produced many possibly useful drugs of these classes, and usually they are first tested on animal tumours or leukæmias. KRAKOFF remarks that success in animals does not guarantee success in man. He gives as examples the glutamine antagonists azaserine (o-diazoacetyl-L-serine) and D.O.N.(6-diazo-5-oxo-L-norleucine) which had a pronounced inhibitory effect on the growth of tumours and transplanted leukæmia in animals but failed to influence human leukæmia appreciably. This difference, too, suggests that "there may be important metabolic differences between leukæmias in man and the various animal systems which have been studied". These differences and those between normal and neoplastic cells have not yet been clearly defined, despite much effort and the accumulation of evidence pointing to their likely existence. All the drugs so far developed act on metabolic pathways common to normal and neoplastic or leukæmic cells, and consequently the drugs will depress or destroy normal tissue if the dose is sufficient; it is the rapid rate of growth and the relative frequency of division of neoplastic and leukæmic cells that enable the drugs to act in lower concentrations.

The other contributions to this symposium deal with more recognised aspects of leukæmia, but two further articles deserve special notice. In their article on clinical manifestations FIRKIN and MOORE[11] mention the question of "pre-leukæmic leukæmia"—a concept originally put forward by BLOCK et al.[12] in 1953. A patient has aplastic or refractory anæmia, neutropenia, or thrombocytopenia, or some combination of these. After some months or years of treatment the picture suddenly changes to that of leukæmia; sometimes there is a preliminary peripheral monocytosis and increased activity in the marrow with the appearance of immature granulocytes; lymph-glands, spleen, and liver may be enlarged. Soon the typical picture of acute leukæmia, commonly of myelocytic type, appears. The course tends to be rapid and fatal, the leukæmia failing to respond to any treatment. The important question is: Do these patients have leukæmia in a form unrecognisable with current diagnostic methods from the onset of their illness, or does the pre-existing hæmatological abnormality predispose them to the subsequent development of leukæmia? FIRKIN and MOORE admit that this question cannot yet be answered, though some suggestive changes were noted by WEYMOUTH et al.[13] in the thymic nucleic-acid pattern of irradiated animals before the development of leukæmia. In the second article HAURANI et al.[14] record failure in 26 attempts to transplant human marrow in 19 patients. 9 patients had acute leukæmia and were given preliminary total body irradiation; 3 patients with acute leukæmia were in an aplastic phase induced by anti-metabolites and received no radiation; 7 patients had aplastic anæmia. The source of the marrow was excised human ribs. 4 other patients—1 with aplastic anæmia and 3 with reticuloses—received infusions of aspirated fresh human marrow; in only 1, who had her own marrow injected after a large dose of nitrogen mustard, was there any effect.

This symposium brings to our notice the impressive amount of fundamental and applied research now in progress in many institutions in the United States. Similar if less extensive work is being carried on in other countries. The large volumes by DAMESHEK and GUNZ[15] and HAYHOE[16] provide digests of the immense amount of information that has been gathered about leukæmia in man and in animals. *Leukæmia Abstracts*[17] summarises each month the contents of 60 or 70 new papers on subjects directly or indirectly concerned with leukæmia. Yet the solution still eludes us; and we are left with the impression, reinforced by this latest symposium, that the most valuable clues may be found in studies of the properties and metabolism of the leukæmic cell—studies which are now being energetically pursued. At the same time the clinician, faced with the immediate problem of the leukæmia patient, must use every clue to better treatment, however empirical the basis, provided he is prepared to change as soon as more rationally designed treatments appear.

10. Krakoff, I. H. *ibid.* p. 735.
11. Firkin, B., Moore, C. V. *ibid.* p. 764.
12. Block, M., Jacobson, L. O., Bethard, W. F. *J. Amer. med. Ass.* 1953, **152**, 1018.
13. Weymouth, P. P., Delfel, N. E., Doell, R. J., Steinbock, H. L., Kaplan, H. S. *J. nat. Cancer Inst.* 1955, **15**, 981.
14. Haurani, F. I., Repplinger, E., Tocantins, L. M. *Amer. J. Med.* 1960, **28**, 794.
15. Dameshek, W., Gunz., F. Leukemia. New York, 1958.
16. Hayhoe, F. G. J. Leukæmia: Research and Clinical Practice. London, 1960.
17. *Leukemia Abstracts*. The Lenore Schwartz Leukemia Research Foundation, Chicago.

Glaucoma

THE various ocular disorders which are grouped together as glaucoma are marked by ischæmia of the distal visual nerve-elements—those either of the retina itself or of the optic nerve. This has long been held to be the end-result of a disturbance of the ocular circulation provoked by causes some of which are apparent (as in many cases of secondary glaucoma) but which mostly are unknown.

In a high proportion of cases of primary glaucoma the cause is thought to be mechanical compression of the nervous tissues or their nutrient vessels—a mechanism which is perhaps most clearly evident in the congestive form of glaucoma where venous congestion and œdema of the ocular tissues are associated with a clear increase of intraocular tension. On the other hand, in the insidious form of primary glaucoma ("simple glaucoma") selective atrophy of bundles and sectors of optic-nerve fibres often proceeds silently without the tension increasing much. Nevertheless, in view of the considerable rise of tension in the advanced stage, pressure is generally believed to be at least the proximate cause of glaucomatous atrophy; and, because at earlier stages tonometry so often shows the pressure to be within normal limits, the accuracy of tonometric methods has been questioned. This has led to the development of more refined methods of tonometry—in particular, the applanation tonometer of GOLDMANN.[1] Another view is that glaucoma may result from disease of the nutrient vessels which renders them vulnerable to normal pressures; and indeed in the unusual "low-tension glaucoma" typical glaucomatous atrophy is found without raised ocular tension. This type has been ascribed to the vascular sclerosis and cavernous atrophy in the optic nerve that was originally described by SCHNABEL[2]; and it now seems probable that similar changes underlie other forms of primary glaucoma. In 1945 LOWENSTEIN and GARROW[3] described a form of spongy degeneration of the optic nerve which they believed preceded the cavernous atrophy; and two years later WOLFF[4] suggested that sclerosis played an important part in the production of optic-nerve ischæmia in primary glaucoma of various types. CRISTINI,[5] employing Pickworth's staining method to examine eyes enucleated in an advanced state of glaucoma, detected diminution in the number of vessels in the capillary network of the papilla and retrolaminar part of the nerve, and concluded that this was the essential pathological change in cavernous atrophy and accounted for the manifestations of glaucoma throughout the eye.

DUKE-ELDER[6] regards the mechanical obstruction of the angle of the anterior chamber—generally believed to be the cause of the raised tension in simple glaucoma—as itself a product of vasosclerosis, probably affecting tissues in the region of the trabecula and canal of Schlemm and thus obstructing the aqueous outflow. Such sclerosis may result directly in ischæmic optic atrophy if it affects chiefly the posterior segment of the eye; or, if the outflow channels are most affected, in hypertension. Thus raised tension, which is irregularly associated with early glaucomatous atrophy, may be but one result of a process which, even without rise of tension, may produce ischæmia; and this ischæmia is further aggravated by the effects of mechanical compression when the intraocular tension rises.

The first result of obstruction of the aqueous exits is accentuation of the normal diurnal pressure variations rather than an absolute rise of tension; and experimental work indicates that this may represent an aberration of a normal homœstatic mechanism. The linear rise in tension observed when an excised eye is perfused with fluid is matched in the living eye by an initial rise followed by a period in which the tension remains static before finally increasing again, as though the intraocular pressure were controlled by a mechanism effective within certain limits but overcome by increasing stress. When the sympathetic nerve-supply to the eye is interrupted the pressure rise resembles that in the excised eye. That this nervous control may be mediated through a hypothalmic centre is suggested by the work of VON SALLMAN and LOWENSTEIN[7] and of GLOSTER and GREAVES.[8] Afferent impulses to this centre are believed to arise in the region of the trabecula, and further work is being undertaken to determine the pathway of vasodilator efferents antagonistic to those of the sympathetic.

In diagnosis measurement of the intraocular tension, however accurate, is less important than observation of its fluctuations, or provocative tests which, by increasing the pressure on the aqueous exit channels or obstructing them further, demonstrate their relative incompetence. All such tests are based on assumptions—for example, the constancy of scleral rigidity, of episcleral venous pressure, and of aqueous formation during tonometry—whose validity is not established. DUKE-ELDER, while admitting that the water-drinking test has a limited value in indicating the competence of the outflow channels, prefers BLAXTER's[9] bulbar compression test to GRANT's[10] tonography for determining organic obstruction at the chamber angle. Assessment of the optic-nerve damage by careful ophthalmoscopy, perimetry, and campimetry remain sheet-anchors in the early diagnosis of simple glaucoma; and unless impaired function is detected by such examinations DUKE-ELDER recommends the withholding of surgical treatment. Miotics (pilocarpine, eserine, and, in emergency, di-isopropylfluorophosphate) remain of value in medical treatment—supplemented in some cases by the carbonic-anhydrase inhibitors, acetazolamide and methazolamide. General measures to improve the systemic circulation are also useful.

1. Goldmann, H. Applanation tonometry. *In* Glaucoma: Transactions of the Second Conference, Dec. 3–5, 1956 (edited by F. W. Newell); p. 167. New York, 1957.
2. *Arch. Augenheilk.* 1892, **24**, 273.
3. Lowenstein, A., Garrow, A. *Amer. J. Ophthal.* 1945, **28**, 240.
4. Wolff, E. *Trans. ophthal. Soc. U.K.* 1947, **67**, 133.
5. Cristini, G. *Brit. J. Ophthal.* 1951, **35**, 11.
6. Duke-Elder, S. *Canad. med. Ass. J.* 1960, **82**, 293.
7. von Sallmann, L., Lowenstein, O. *Amer. J. Ophthal.* 1955, **39**, 11.
8. Gloster, J., Greaves, D. P. *Brit. J. Ophthal.* 1957, **41**, 513.
9. Blaxter, P. L. *ibid.* 1953, **37**, 641.
10. Grant, W. M. *Arch. Ophthal.* 1950, **44**, 204.

Annotations

DIAGNOSIS OF GUILLAIN-BARRÉ SYNDROME

THE diagnostic criteria of the Guillain-Barré syndrome are discussed by Osler and Sidell,[1] who point out that the nosological characteristics of this condition, as described by Guillain, Barré, and Strohl in 1916 [2] and amplified by Guillain in 1936,[3] are relatively stereotyped. But many case-reports and reviews have included cases which did not fulfil these diagnostic criteria, with the result that modern views concerning the clinical features and prognosis of the illness have become clouded.

Having reviewed the findings in a series of 10 personal cases, Osler and Sidell agree with Petch,[4] who pointed out that the condition usually follows a febrile illness, and gives rise to symmetrical flaccid paralysis with abolition of the tendon reflexes and with pronounced subjective sensory symptoms but without much objective sensory loss. Probably this condition accounts for most cases of ascending (Landry's) paralysis. Invariably the cerebrospinal-fluid protein is increased without any increase in cells. Occasionally death ensues, but most patients recover completely. In the cases described by Osler and Sidell the muscular weakness usually began in the proximal muscles of the legs and later affected the arms, though rarely it began more distally. Facial weakness, either unilateral or bilateral, was common, but other cranial nerves were unaffected; retrobulbar neuritis was not observed, and papillœdema was occasionally found later in the illness, and was probably related to the very high protein content of the cerebrospinal fluid. Bladder and bowel control was never directly affected, although there was sometimes transient difficulty in voiding urine—presumably due to immobility and weakness of the abdominal muscles. In most cases, improvement began before the third week of the illness and continued without relapse. Of the 10 patients 7 recovered completely; 3 died, but in each of these cases death appeared to be due to age or unrelated disease and was not attributable to the primary illness.

Osler and Sidell observe the criteria applicable to the syndrome originally described by Guillain and his colleagues; but it now seems doubtful whether this condition is a distinct clinical and pathological entity. The disorder is still commonly referred to as "acute infective polyneuritis"; but it is becoming increasingly apparent that it is due, not to an infective agent which invades nervous tissue, but to an allergic or hypersensitivity response, affecting particularly the spinal roots, and usually following an infection. Hence the title "postinfective polyneuropathy" or "polyradiculopathy" is preferable. The improvement which follows treatment with steroids, and the relapse which may follow their premature withdrawal, supports this concept.[5] The fact that many cases of subacute or relatively indolent polyneuropathy for which no other cause can be found [6] respond strikingly to similar treatment seems to suggest that our ideas of the clinical criteria for the diagnosis of "postinfective polyneuropathy" should be broadened in order to embrace many cases which run a subacute or even a chronic course and which vary in their clinical form. Probably a satisfactory compromise would be to retain the eponymous "Guillain-Barré syndrome" to identify that form of the condition which is defined by Osler and Sidell [1] but to apply the more comprehensive title of "postinfective polyneuropathy" to the steroid-responsive cases which run a subacute or chronic course.

1. Osler, L. D., Sidell, A. D. *New Engl. J. Med.* 1960, **262**, 964.
2. Guillain, G., Barré, J. A., Strohl, A. *Bull. Soc. méd. Hôp. Paris*, 1916, **40**, 1462.
3. Guillain, G. *Arch. Neurol. Psychiat., Chicago*, 1936, **36**, 975.
4. Petch, C. P. *Lancet*, 1949, ii, 405.
5. Jackson, R. H., Miller, H., Schapira, K. *Brit. med. J.* 1957, i, 480.
6. Austin, James H. *Brain*, 1958, **81**, 157.

AFRICAN HORSE SICKNESS

African horse sickness is a virus disease spread by the bites of blood-sucking insects, usually species of culicoides. In the fully susceptible horse it produces an acute illness characterised by hyperthermia, œdema of the lungs, pleura, and subcutaneous tissues, and bleeding into the internal organs; and the mortality-rate may exceed 90%. Mules are less susceptible, and donkeys, though they may be infected, rarely die of the disease. There is no evidence that the virus will infect man. The condition is normally confined to South and East Africa, but occasional severe epizootics are known to have occurred in Egypt and the Middle East, including the Yemen and the Red Sea coast of Arabia. Recent reports from seven countries in the Near and Middle East indicate that a severe epizootic is now in progress, and there are indications that the disease may, for the first time on record, spread into India and Asia.

Control of the disease is complicated by the existence of several serologically distinct types of virus, all of which are capable of producing symptoms in horses, although there may be minor differences between the severity of the illness produced by different serotypes. It is now believed that there are seven immunologically different types, and that there may be fairly wide strain differences within each serotype. Infection with a virus confers lasting immunity to other strains of that type, but the horse may still be infected with another virus of a different type. All strains will infect mice inoculated by the intracerebral route; and it is possible, by serial passage in mice, to produce an attenuated virus which will act as an effective vaccine. A polyvalent vaccine containing representative strains of all seven types has been developed in South Africa, where it has proved to be an extremely efficient means of prophylaxis and control.

The last outbreak of African horse sickness outside the normal limits of the enzootic area affected the Sudan, Egypt, and Palestine in 1944. On that occasion it was shown that virus strains isolated in Egypt and Palestine were very closely related to each other and also to two strains included in the standard polyvalent South African vaccine. Vaccination of horses and donkeys in the affected area completely controlled the epizootic, deaths ceasing about three weeks after immunisation. Preliminary reports from the Onderstepoort Veterinary Research Laboratories indicate that the virus responsible for the present outbreak is antigenically different from strains previously studied, but the extent of this difference is not yet known. If the new virus is much different from the seven types included in the vaccine then it is quite possible that the present polyvalent vaccine would be ineffective in controlling the disease. Almost certainly a vaccine could be prepared against the new Asian strain, but this will take time. Meanwhile it is worth remembering that other means of control are not to be overlooked. Strict control of the movement of horses, mules, and donkeys should help to localise the disease, and insecticides can be used to reduce the risk of bites by

culicoides. Alexander [1] reported that stabling of horses at night under the protection of smoke-screens seemed to offer definite protection in areas where supplies of vaccine were not available and where better insect repellants were unobtainable. Such simple measures may be invaluable in rural areas where horses are still of major economic importance.

It is not at all clear how epizootics such as the present one originate. Direct insect spread from horse to horse can occur, but it is unlikely that the reservoir of infection is either in horses or in culicoides. Rodents and other wild animals have been examined, but there is no evidence that they play any part in the life cycle of the virus such as that played by monkeys in the jungle cycle of yellow fever. Infection can be introduced into an area by infected horses, mules, or donkeys; this was thought to be the case in the 1944 outbreak in Egypt. Another danger is that infected culicoides may be carried considerable distances by aircraft. These insects are attracted to light, and could well enter fully lighted aircraft at night and be carried from the enzootic area to previously clean regions. International sanitary regulations should preclude all such risks, but anyone who has travelled widely in tropical countries knows how perfunctory is the spraying of passenger planes on most occasions.

One encouraging side to the present problem is the speed with which it has been tackled by international organisations. The Food and Agriculture Organisation of the United Nations has planned a campaign to cover the whole affected area, and an informal conference of directors of the veterinary services of the countries is to be held in August. This cooperative plan will provide an opportunity to investigate some of the obscure points about this important veterinary disease.

CONGENITAL DEFECTS OF THE FEMUR

CONGENITAL defects of the femur vary from simple hypoplasia of the bone to complete absence. These defects most commonly affect the upper end of the bone, and Golding [2] pointed out that congenital short femur and congenital coxa vara are probably variations of the same underlying abnormality. Ring [3] has shown that femoral growth may be defective in the absence of radiological changes, although more commonly there is either broadening of the upper epiphyseal cartilage or some bowing of the bone. Major defects in development are most commonly associated with changes at the upper end of the femur, and this type of disorder has been studied by Morgan and Somerville.[4] Serial studies of such cases, or exploratory operation, show that the defect is one of ossification, and the cartilaginous primordium is always present. It is remarkable how often in these patients the head of the femur develops in a normal acetabulum, but separated from the shaft by a broad band of cartilage in which ossification is delayed and in which a progressive varus deformity may develop. Morgan and Somerville distinguish two types of varus deformity in these patients. In the first the lesion is distal to the trochanter and growth is greatly impaired; in the second it is proximal to the trochanter and the deformity is progressive, but growth is almost normal.

The prognosis in children with congenital defects of femoral development can be assessed at an early age by measuring the apparent growth of both femora. The depression of growth remains constant throughout childhood, and a femur which is only 50% of the length of its fellow at birth retains a similar relationship until maturity. Shortening of the leg may therefore be extreme; and there is every reason to correct this as much as possible, either by osteotomy to correct deformity, by grafting to prevent progressive varus, or by bone lengthening.

1. Alexander, R. A. *Onderstepoort J. vet. Sci.* 1948, **23**, 77.
2. Golding, F. C. *J. Bone Jt Surg.* 1948, **30B**, 161.
3. Ring, P. A. *ibid.* 1958, **41B**, 73.
4. Morgan, J. D., Somerville, E. W. *ibid.* 1960, **42B**, 264.

DELIRIUM

THE word delirium derives from the era of descriptive symptomatology. It is still used to describe confusional states, usually with an element of restlessness and irritability. The condition can range from mild disorientation to gross confusion and hallucinosis, anxiety being a common accompaniment. The more severe forms, classically associated with general infections, used to be called "toxic confusional insanities"—a good descriptive term.

Delirium can now be viewed with a more analytic eye. Two approaches have been made to interpret the symptoms in terms of cerebral function. On the one hand certain elements of the delirium may be viewed as reflecting dysfunction of particular parts of the brain: thus agnosia, dysphasia, amnesia, and auditory or visual hallucinations may be recognised as components of the delirium. This approach to the study of confusion was illustrated by Patterson and Zangwill [1] among others. Another example is the Korsakoff syndrome, where the confusional state is notable for the breakdown in memory mechanisms and the orientation of memories in correct temporal sequence. The evidence points to disorder in the hypothalamic region or its interconnections with the frontal lobes as the common causal factor here; thus a lesion in this situation must be considered when temporal disorientation is a distinct feature of delirium.

Such an analysis does not provide information on the nature of the cerebral abnormality, which may be biochemical and easily reversible, or organic and irreversible. Recognition of features of the delirium or accompanying symptoms may suggest a specific primary cause; and this provides the second interpretive approach. One example is acute liver failure with its characteristic "flapping tremor" and often fluctuating confusion, in which a rise in blood-ammonia seems to be an important causal factor. The delirium of myxœdema, described many years ago, has attracted renewed interest. Thiamine deficiency, hypoglycæmia, porphyria, atropine poisoning, and some forms of subacute combined degeneration (vitamin-B_{12} deficiency) at times give rise to a syndrome of delirium with diagnostically characteristic symptoms and signs. Simple dehydration, electrolyte imbalance, and failure of cerebral oxygenation, whether from cardiac or pulmonary causes or peripheral interference, may also give rise to delirium, as may intracranial lesions either by general changes in intracranial pressure or by more direct interference with particular cerebral structures. Thus, looked at in this way, delirium is a manifestation of widely differing disease entities, of which the common factor—usually biochemical—is dysfunction of the brain.

A different point of view is that of Engel and Romano,[2] who seek to unify delirium as a "syndrome of cerebral insufficiency" akin to renal, cardiac, or hepatic insuffi-

1. Patterson, A., Zangwill, O. L. *Brain*, 1944, **67**, 54.
2. Engel, G. L., Romano, J. *J. chron. Dis.* 1959, **9**, 260.

ciency. This is an interesting approach; but is it tenable? Cerebral function is not unitary in the sense that cardiac or (within limits) renal or hepatic function is unitary. Some cerebral structures may function while others are in abeyance, with diverse effects on mentation. Even biochemically (as Engel and Romano themselves observe), different parts of the brain may require different milieux for efficient functioning. While it is true that the electroencephalogram rhythms slow characteristically in delirium, it is also true that such slowing may have a variety of clinical causes. The important differential diagnosis is not between delirium and conditions such as depression, hysteria, or unusual forms of schizophrenia, which may occasionally present in a similar way, but between the varying causes of delirium itself. The need is to analyse rather than unify this symptom—or perhaps congeries of symptoms.

GERM-FREE ANIMALS

THE gallant at the court of Charles II might spend his afternoon at his choice in writing verse or playing the viol or in "some chymical experiments". Most of Darwin's work was done with eyes and fingers in his study or the greenhouse at Downe. Today—although the chief tool of research is still the forebrain—the opportunities for scientific investigation are more and more limited by the complexities of method and apparatus. In this respect the study of the germ-free animal is almost as difficult and expensive as atomic physics. It demands premises designed for the purpose, equipment which cannot be improvised from the store-room, and a large team of devoted workers with no other call on their time. So it is that there are not more than half a dozen institutes where this subject is pursued; but the slow advance in knowledge has at least the advantage that we can absorb it deliberately and thoughtfully.

The third volume of the Lobund Reports from the University of Notre Dame is therefore a welcome event.[1] The greater part is devoted to the germ-free chicken. In general the germ-free and conventional birds show no difference in weight for age and in rate of growth. Those organs which in the conventional bird are in close contact with bacteria (e.g., the intestines and their associated lymph-glands) are smaller in the germ-free bird, which also has fewer circulating lymphocytes. There are minor differences in the aminoacid content of the bowel. The germ-free bird produces no antibodies to the intestinal bacteria found in the conventional bird, unless autoclaved cultures of these are fed to it for some weeks. Similarly it produces antibodies to the bacteria which are abundant in its autoclaved diet. As judged by these and other immune reactions, it is as capable of forming antibodies as the conventional bird. Fed on a "complete" synthetic diet, it shows no obvious signs of vitamin deficiency. These findings are not unlike those already reported in germ-free mammals; but the many tedious experiments are a necessary prologue to any further work, and this no doubt is already in hand. A more original study is on the presence of protozoa and helminths in germ-free rats, mice, guineapigs, chickens, and dogs. There are none—except in the dogs, and it has long been known that puppies could be infected by maternal nematodes in utero. A tribute to R. W. Glaser is well deserved: it was he who first raised protozoa and insects free from bacteria, and, as with many pioneers, the value of his work was not well recognised until after his untimely death.

To the practising doctor the most rewarding aspect of the study of the germ-free animal will probably be the mechanism of bacterial infection. Nobody believes any longer that infection is of the nature of a chemical equation: host + parasite = disease. Here and there we are getting hints which make it clear that the process is something far more complicated. The germ-free animal has already played a part in this newer knowledge, and we can expect even more to come now that the spadework has been done by the teams at Notre Dame and elsewhere. If there is a danger, it is as much semantic as pathological. Is a germ-free rat a rat at all? That picturesque and painful jellyfish the Portuguese man-of-war is thought to be a symbiosis of four or five distinct organisms: one swims, another catches, another digests, and so on. It could be argued that the rat is not dissimilar in a state of Nature: one organism to move and fight and breed, and a million others to make the vitamins and protect the skin and mucous membranes against infection. Is it a rat or a symbiosis?

1. Lobund Reports, no. 3. University of Notre Dame, Notre Dame, Indiana. 1960. Pp. 182. 5$.

CIGARETTE-SMOKING AND PULMONARY FUNCTION

IN sporting circles it has long been held that cigarette-smoking impairs lung function, and this belief has been scientifically endorsed by Wilson and his colleagues.[1] These workers compared the results of lung-function studies in 14 persons who had never smoked with those in 14 persons who had smoked at least 20 cigarettes a day for a mean period of 18 years. Preliminary screening excluded from the investigation anyone with symptoms or signs of respiratory disease or with an index of pulmonary mixing greater than 2·5% (the upper limit of normal according to Darling et al.[2]); and each smoker was paired with a non-smoker of like body-surface, height, age, and environmental background.

In the smokers, as compared with the non-smokers, there was a significant decrease in the one-second forced expiratory volume, total lung capacity, maximum breathing capacity, total lung diffusing capacity, and mean membrane diffusing capacity, and a significant increase in the index of pulmonary mixing and in the ratio of residual volume to total lung capacity. The pulmonary capillary blood-volume in the two groups was similar, and the carbon-monoxide concentration in the blood of smokers was not high enough to affect diffusion tests.

These results confirm the observation by Blackburn et al.[3] that cigarette-smoking eventually depresses pulmonary function, and Wilson et al. suggest that the conflicting findings of Turley and Harrison[4] may be explained by, among other things, the fact that these workers investigated students with only short smoking histories. Wilson et al. warn us that in evaluating the results of pulmonary function tests in the individual patient the smoking history should be taken into account, and they suggest that "normal" standards of pulmonary function established by studies in which the subjects tested included cigarette-smokers may have to be revised.

1. Wilson, R. H., Meador, R. S., Jay, B. E., Higgins, E. *New Engl. J. Med.* 1960, **262**, 956.
2. Darling, R. C., Cournand, A., Richards, D. W., Jr. *J. clin. Invest.* 1940, **19**, 609.
3. Blackburn, H., Brožek, J., Taylor, H. L. *Ann. intern. Med.* 1959, **51**, 68.
4. Turley, F. C., Harrison, T. R. *Amer. J. med. Sci.* 1932, **183**, 702.

Public Health

POLIOMYELITIS IN THE VACCINATED
ENGLAND AND WALES, 1958

T. J. GEFFEN
M.D. Lond., M.R.C.P.
MEDICAL OFFICER, MINISTRY OF HEALTH

C. C. SPICER *
M.R.C.S.
OF THE EPIDEMIOLOGICAL RESEARCH LABORATORY, CENTRAL PUBLIC HEALTH LABORATORY

WHEN poliomyelitis vaccine became available in this country in 1956 it was decided to keep as complete a record as possible of all cases of poliomyelitis in people who had previously had the vaccine. The total numbers of such cases reported to the Ministry of Health in 1956 and 1957 are recorded in the annual reports of the chief medical officer (Ministry of Health 1957, 1958), but it was not certain that all cases had been reported. In 1958, therefore, an attempt was made to investigate the vaccination history of each case of poliomyelitis formally notified to the General Register Office. This was successful and it seemed justifiable to review the figures and to draw conclusions from them if possible.

Methods of Investigation

Special record cards for each case of poliomyelitis notified during 1958 were completed by the medical officer of health of the sanitary district concerned, with particular reference to any previous history of vaccination against poliomyelitis. For vaccinated patients, the information recorded included their age, the date or dates of vaccination and of onset of the disease, the site of inoculation, and the batch of vaccine used. Information about the site and severity of paralysis was obtained from the hospital to which the patient was admitted or from the general practitioner.

TABLE I—AGE AND SEX DISTRIBUTION OF VACCINATED SUBJECTS WHO LATER HAD POLIOMYELITIS

		Age (yr.)					
		0–4	5–9	10–14	15–19	20+	Total
Paralytic:	Male ..	32	31	11	..	1	75
	Female ..	31	19	6	..	6	62
	Total ..	63	50	17	..	7	137
Non-paralytic:	Male ..	19	41	21	1	1	83
	Female ..	5	8	8	..	1	22
	Total ..	24	49	29	1	2	105
	Total ..	87	99	46	1	9	242

For notification purposes, the General Register Office regarded the year 1958 as the 53-week period from Dec. 29, 1957, to Jan. 3, 1959. All cases notified in this period, irrespective of the actual date of onset of illness, were included. The total number of cases of poliomyelitis reported from each district was checked at intervals against the Registrar-General's corrected notification figures and any discrepancies were investigated. The final correspondence between the two sets of figures was close, reports having been received for more than 95% of the cases notified.

* Now with the Imperial Cancer Research Fund, 48, Lincoln's Inn Fields, London, W.C.2.

Results

Altogether 242 cases of poliomyelitis (137 paralytic, 105 non-paralytic) were reported in vaccinated persons. This represents about 12% of the corrected notifications received by the General Register Office in 1958, which totalled 1994 (1419 paralytic, 575 non-paralytic). 64 had had only one dose of vaccine, 173 had had two doses, and 5 had had three doses. 4 patients died; of these 1 had had one dose and 3 had had two doses of vaccine. (The total number of deaths from acute poliomyelitis in the year was 129.)

The age and sex distribution of the cases is shown in table I. The location of the paralysis with reference to the limb of inoculation is shown in table II, which also distinguishes between cases which started less than 28 days after the most recent dose of vaccine and those of later onset. In two instances illness started within 28 days of both the first and second injections; in the tables these are related to the most recent inoculation.

In table III the 137 paralytic cases are set out to show the proportion in which the inoculated limb was affected in the under-28-day group, compared with that for the 28-day and over group.

TABLE III—PARALYTIC POLIOMYELITIS: SITE OF PARALYSIS, AND TIME BETWEEN INOCULATION AND ONSET OF ILLNESS

Days after inoculation	Paralysis including inoculated limb	Paralysis not including inoculated limb
0–27 days	13 (24·1%)	41
28 days or more ..	17 (20·5%)	66

Of the 13 patients in whom the inoculated limb (left arm in each instance) became paralysed within 28 days of inoculation, 10 had had one dose, 2 had had two doses, and 1 had had three doses of vaccine. Paralysis of the left arm was only a part (often relatively minor) of a more widespread paralysis in 8 patients. In the other 5 the left arm was the only, or only important, site of paralysis. 2 of the 17 patients who developed weakness of the inoculated limb 28 or more days after inoculation had had only a single dose and 15 had had two doses. In 4 of these 17 patients the inoculated limb was the only, or only important, site of paralysis.

Table IV shows the distribution of cases, both paralytic and non-paralytic, at various periods after inoculation with a second or third dose of vaccine. Tables V and VI break down further all the cases which became paralytic before the 28th day.

Discussion

The figures reported here were not part of a controlled trial of the efficacy of poliomyelitis vaccine. They show the number of cases of poliomyelitis diagnosed in vaccinated people but comparison with the prevalence in the unvaccinated population is open to the objection that the two groups may not be similar and that the size of the

TABLE II—DISTRIBUTION OF CASES OF POLIOMYELITIS BY NUMBER OF DOSES OF VACCINE, TIME OF ONSET OF ILLNESS AFTER VACCINATION, AND SITE OF PARALYSIS

1 dose						2 or more doses						Total
Paralytic				Non-paralytic		Paralytic				Non-paralytic		
0–27 days		28 days or more		0–27 days	28 days or more	0–27 days		28 days or more		0–27 days	28 days or more	
10*	29†	2*	4†	16	3	3*	12†	15*	62†	10	76	242

* Inoculated limb was involved. † Inoculated limb was not affected.

vaccinated group cannot be precisely estimated. Nevertheless, it seems justifiable to relate the incidence of the disease in vaccinated children to that in non-vaccinated children, and to see if the comparison provides confirmatory evidence of the protective action of the vaccine, previously shown in controlled trials (Medical Research Council 1957, Poliomyelitis Vaccination Evaluation Centre 1955).

It has been shown (Geffen 1950, Martin 1950, McCloskey 1950) that poliomyelitis with paralysis localised to the limb of inoculation will occasionally follow immunisation, and this risk has been assessed for certain prophylactics (Medical Research Council 1956). It is conceivable that poliomyelitis vaccine itself might be associated with such "provocation" paralysis; our figures can be used to assess this risk.

In 1955 an outbreak of poliomyelitis in the United States was attributed to a batch of vaccine containing live virus. Our data can also be used to investigate the possibility of such an effect on the incidence of poliomyelitis in England and Wales in 1958.

"*Provocation*" *Paralysis*

A report from the Medical Research Council (1956) showed that where cases of "provocation" paralysis might be associated with a prophylactic, the risk could be measured by comparing the number of cases of paralytic poliomyelitis in the first 28 days after inoculation with the number in each subsequent month.

Such a comparison is liable to error when the prophylactic is poliomyelitis vaccine itself because, if the vaccine confers a measure of protection, more cases are likely in the period shortly after vaccination than later, when an appreciable level of immunity has been acquired. Therefore the probable protective action of the vaccine must be taken into account in discussing the possibility of provocation paralysis. One approach lies in considering the site of paralysis.

TABLE IV—TIME OF ONSET OF POLIOMYELITIS AFTER LAST DOSE OF VACCINE (TWO OR MORE DOSES ONLY)

—	Days after last inoculation			
	0–27	28–55	56–83	84 or more
Paralytic ..	15	12	8	57
Non-paralytic ..	10	14	3	59
Total ..	25	26	11	116

If a provocation risk exists, one would expect to find paralysis of the inoculated limb in a proportionately higher number of paralytic cases during the first month than in later months. Table III shows that the incidence of inoculated-arm paralysis in the cases occurring within 28 days was only slightly greater than in those notified 28 or more days later, the difference being without statistical significance.

Again, if an excess of cases in the first month was due to a provocation effect, one would expect a striking drop during the second month, with the figures for the third and later months being similar to those for the second. Table IV shows that the difference between the first and second 28-day periods is small and that during the third period the reduction is greater. This is compatible with a protective effect which requires a few weeks to develop fully, and is against a provocation effect.

The distribution of cases during the first 28 days provides further evidence against provocation. The Medical Research Council report (1956) showed that the heaviest incidence of provocation cases was in the 7–13 days after inoculation. Table V shows that, in the cases now under review, during the first month the incidence was somewhat higher in the first 7-day period than in the second 7-day period; this does not suggest a provocation effect.

TABLE V—INTERVAL IN 7-DAY PERIODS BETWEEN VACCINATION AND ONSET OF POLIOMYELITIS (PARALYTIC CASES ONLY)

—	Days after last inoculation				
	0–6	7–13	14–20	21–27	Total
Complete course	7	5	2	1	15
One dose only	15	13	4	7	39
Total ..	22	18	6	8	54

Finally, among the 13 "included" cases are all those in which the inoculated limb became paralysed, whether the paralysis was slight or severe and whether or not other sites were equally or more affected. In a true "provocation" paralysis one would expect the inoculated limb either to be the only site of weakness or at least the first and major one. This was true in only 5 cases, and such an incidence, over a period during which some 13,000,000 doses of vaccine were given, provides a strong argument against a provocation effect.

This accords with experience in the Chicago outbreak of 1956, in which a provoking effect could not be demonstrated (Nathanson et al. 1959).

"*Inoculation*" *Poliomyelitis*

In 1955 a number of cases of poliomyelitis in California and Idaho followed the use of a vaccine containing live virus (the Cutter incident).

Langmuir et al. (1956) showed that when poliomyelitis developed in an inoculated person, the onset was most frequently during the 4–11 days inclusive after inoculation, and that in about two-thirds of the paralytic cases the inoculated limb was the first site of paralysis. Although the results of our investigation provide no evidence for provocation paralysis, table V shows that paralytic disease during the first 4 weeks after inoculation was appreciably more frequent in the first 2 weeks than in the second 2 weeks. The difference was observed both after a first inoculation (28 out of 39 cases) and after a second (12 out of 15 cases). Therefore it is important to see whether this difference is an indication of inoculation poliomyelitis.

The features suggesting inoculation poliomyelitis would be an association of most of the cases with a single batch, or only a very small number of batches, of vaccine; a particular prevalence of paralysis in the limb of inoculation; and a concentration of cases during the 4–14 days after inoculation.

It has already been shown that the site of inoculation did not correlate with the site of paralysis in these cases. Similarly there is no correlation with a single batch of vaccine. The cases were distributed between twenty-two of the thirty batches of vaccine used during the year and

TABLE VI—INTERVAL BETWEEN INOCULATION AND ONSET OF ILLNESS (PARALYTIC CASES ONLY)

—	1st week	2nd week	3rd week	4th week
Days after inoculation	0, 1, 1, 1, 1, 1, 1, 1, 2, 2, 2, 2, 3, 3, 3, 4, 4, 4, 5, 5, 5, 5	8, 8, 8, 8, 8, 8, 8, 9, 9, 10, 10, 10, 11, 11, 12, 12, 13, 13	14, 15, 16, 16, 17, 19	22, 22, 23, 23, 23, 24, 25, 25
Total ..	22	18	6	8

In a few cases the exact day the illness started, and hence the interval between inoculation and onset, is in doubt. In these the most probable interval has been taken.

TABLE VII—POLIOMYELITIS IN 1958 CLASSIFIED BY PRESENCE OR ABSENCE OF PARALYSIS AND BY VACCINATION STATE (CHILDREN UNDER 15)

Unvaccinated			Once vaccinated			Twice (or more) vaccinated		
Paralytic	Non-paralytic	Ratio paralytic/non-paralytic	Paralytic	Non-paralytic	Ratio paralytic/non-paralytic	Paralytic	Non-paralytic	Ratio paralytic/non-paralytic
829	326	2·54	42	19	2·21	88	83	1·06

between all of the six manufacturing firms which provided vaccine, including the British vaccine in which the Mahoney strain of type-1 virus is not used.

As regards time of onset, despite the concentration of cases in the first fortnight, the preponderance in the 4–14 day period is small, affording little support for the idea of inoculation poliomyelitis. 26 of the 54 cases fell in this 11-day period, whereas if the distribution had been even throughout the 28-day period, 21 cases should have done so. Thus inoculation poliomyelitis does not account for the excess of cases in the first 2 weeks.

A period of prevalence of poliomyelitis in a district is likely to lead to an increased demand for vaccine and among those vaccinated there may be a small number of contacts who are already incubating the disease. This could increase the proportion of cases within the first fortnight. Although this explanation cannot readily be confirmed, it does seem reasonable.

Efficacy of the Vaccine

Even by the end of 1958 less than 5% of those born before Jan. 1, 1943, had been inoculated against poliomyelitis. In assessing the efficacy of the vaccine, it would therefore be misleading to include the older patients, of whom there were only 10, and the following figures relate only to patients born in 1943 or later.

The first difficulty is to arrive at a figure for the vaccinated population in this age-group, as the numbers changed from some 1,400,000 at the beginning of 1958 to about 6,000,000 at the end. To use the latter figure would give a grossly exaggerated impression of vaccine efficacy, and to take the mean of the two would ignore the wide variations in speed of the vaccination programme during the year. It seemed reasonable, therefore, to take the time when half the cases of poliomyelitis had been notified, and to accept the number then immunised as the vaccinated population for the year.

Objections to this course are that:

1. Possible differences in the relation between the local incidence of poliomyelitis and local degrees of progress with vaccination programmes are ignored.

2. The weekly uncorrected notification figures are used, and the correction rate is likely to be rather higher during periods when poliomyelitis is prevalent than earlier in the year.

3. The weekly notifications refer to patients of all ages, and the proportion of those over and under 15 years might be slightly different before and after the date by which half the notifications had been received.

4. The number of notifications in all patients from birth to the age of 15 is related to the number of cases in vaccinated subjects, who, to be eligible for vaccine, had to be over 6 months old and to have been born after Jan. 1, 1943 (hence a few could have been nearly 16 if they became ill towards the end of 1958).

Accepting these possible sources of error, none of which is likely to be large, incidence-rates were calculated. Half of all the uncorrected notifications for 1958 (slightly under half the paralytic, and slightly over half of the non-paralytic cases) had been received by the week ending Aug. 30. On Aug. 31 almost exactly half the eligible population had had one or more doses of vaccine (out of about 10,740,000 children, 4,980,000 had had two or more doses and a further 360,000 had had one dose of vaccine). During the year there were among the under-15-year-old population 232 cases of poliomyelitis in the vaccinated population and 1155 cases in the unvaccinated population. The respective incidence-rates are 4·3 per 100,000 in the vaccinated and 21·4 per 100,000 in the unvaccinated. If children who had received only one dose are included in the unvaccinated population, the respective incidence-rates are 3·4 per 100,000 in the vaccinated and 21·1 per 100,000 in the unvaccinated. So far as the validity of the calculations can be accepted, these figures are in keeping with the previously published estimates of vaccine efficacy in controlled trials (Medical Research Council 1957, Poliomyelitis Vaccine Evaluation Centre 1955).

35 children under 15 died from acute poliomyelitis during the year. 3 had had vaccine (only a single dose in 1 case) and 32 had not had vaccine. Using the same figure as before for the vaccinated population in this age-group, the fatality-rate is over ten times as high in the non-immunised children.

One effect of the vaccine may be to decrease the ratio of paralytic to non-paralytic cases, and though this is an indirect measure, it does avoid the various assumptions, with their inherent errors, made in the previous calculations.

The relevant figures (table VII) show that the proportion of paralytic to non-paralytic cases is similar in the unvaccinated and in those who had had only a single dose of vaccine, and is only about half as great in those who had had two or more doses of vaccine. This difference seems to provide further support for the efficacy of the vaccine, provided that two or more doses have been given.

Summary and Conclusions

Information was sought in all notified cases of poliomyelitis in England and Wales during 1958, in people who had had poliomyelitis vaccine. The records have been analysed with respect to the presence of paralysis, its site with reference to the site of inoculation, and the interval between inoculation and the onset of illness.

The figures do not suggest that the vaccine caused "provocation" paralysis or "inoculation" poliomyelitis.

The results provide confirmatory evidence of the efficacy of two or more doses of vaccine as a protection against poliomyelitis.

REFERENCES

Geffen, D. H. (1950) *Med. Offr.* **83**, 137.
Langmuir, A. D., Nathanson, N., Hall, W. J. (1956) *Amer. J. publ. Hlth*, **46**, 75.
Martin, J. K. (1950) *Arch. Dis. Childh.* **25**, 1.
McCloskey, B. P. (1950) *Lancet*, i, 659.
Medical Research Council (1956) *ibid.* ii, 1223.
— (1957) *Brit. med. J.* i, 1271.
Ministry of Health (1957) Report for 1956, part ii, 80.
— (1958) Report for 1957, part ii, 88.
Nathanson, N., Thrupp, L. D., Hall, W. J., Langmuir, A. D., Connell, R. G., Forrester, H. E., Church, R. E., Hall, J. B., Hildebrand, M., Shaugnessy, H. J., Morrissey, R. (1959) *Amer. J. Hyg.* **70**, 107.
Poliomyelitis Vaccine Evaluation Centre (1955) *Amer. J. publ. Hlth*, **45**, no. 5, part 2.

Special Articles

THE CONVERSION OF GENERAL WARDS INTO PRIVATE WARDS

RUPERT VAUGHAN HUDSON
F.R.C.S.

CONSULTANT SURGEON TO THE MIDDLESEX HOSPITAL, LONDON, W.1

STAPHYLOCOCCAL infection in hospital has become more dangerous with the spread of phage-type 80/81, which is both highly infective and highly resistant to antibiotics, and, unlike other staphylococci, remains a long time in the anterior nares of carriers. Hospitals bear a heavy responsibility for seeing not only that their patients are not exposed to this or other infections but also that the public is not infected by carriers discharged from the wards.

Hospital infection often spreads from one patient to another, either directly or through an intermediary carrier. The infecting patient may be admitted for a septic lesion (e.g., an empyema), or may have some incidental infection such as pustules or a boil. From such a person the organism may quickly spread to fellow patients, or to nurses or other personnel who can carry it all over the hospital. On other occasions the infection comes from doctors or nurses handling a patient when they themselves have a whitlow or boil—sometimes one which is apparently so trivial as to be ignored.

Once established in a patient—in his sputum or on his skin or in an infected wound—the staphylococcus very soon infects the whole of his bedding and the bed curtains around him. Despite all our investigations, we still know of no way of preventing a patient from spreading his infection to others in the same ward. Effective isolation is impossible; and sometimes the only way of stopping a ward epidemic is to close the ward.

OPEN WARD OR PRIVATE WARD?

The truth is that the open ward is an anachronism. It is socially undesirable and medically unsound. In 1960 the public, the doctor, and the nurse should no longer be expected to put up with this scandalous impromptu.

What people would like best would be to have the full resources of modern medicine, with skilful nursing, provided for them twenty-four hours a day in their own bedroom at home. Failing this, those who can afford to do so seek admission to a private room attached to a hospital or in a nursing-home. What they actually get is usually poor accommodation; but there are some very real advantages.

The first and most important advantage is the much smaller risk of infection. A private room with special nurses provides the complete form of barrier nursing; and even where the same nurses, orderlies, and wardmaids serve the same private rooms, and the hospital porter visits all and sundry, conveyance of infection (other than influenza and other specific fevers) is comparatively rare. But the private room also avoids some of the grave disadvantages of the public ward:

(1) The *lack of privacy* (a) for the patient, (b) for the relatives visiting the patient, and (c) for the doctor's taking of a personal history or undertaking investigations or treatment.

(2) The *noise*.—In a public ward the auditory assault is continuous—whether from conversation, whispered consultation, the sound of feet and trolleys, the recovery from anæsthesia, the complaint of pain or fear, or such unpleasant necessities as eructation and passage of flatus.

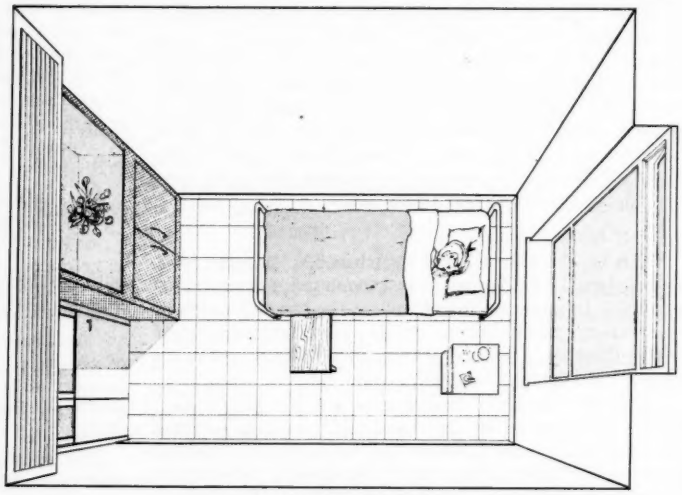


Fig. 2—Bird's-eye view.

(3) The *lights*.—The visual assault is as great as the auditory. Early in the evening the whole ward is plunged into darkness so that the most seriously ill can try to get rest. But during the admittance of emergencies the whole ward may be in a turmoil, enhanced by the switching on of essential lights.

(4) The *lack of sleep*, arising not only from the patient's own anxiety or illness but additionally and unnecessarily from his hospital surroundings and regimen.

(5) The wholesale use of *sleeping-tablets* as symptomatic treatment for these defects in medical care.

It is the custom for a sick horse to be segregated to a loosebox, an orphaned lamb to the kitchen, a sick dog at times to the best bedroom. But our patients are put in large domitories, and obliged to adjust themselves to endure—sometimes for the first time—an intensely public life with many discomforts which are in no way essential for their investigation or treatment. Many of them, admittedly, enjoy the experience, because they are thoroughly sociable; and we are often told that, because of the herd instinct, patients in private wards may feel isolated from their fellows. I agree

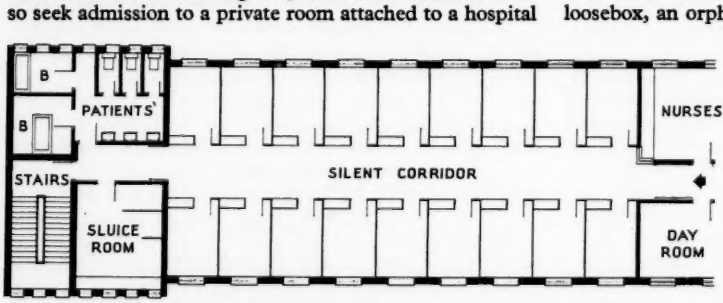


Fig. 1—A typical hospital ward converted to 18 private wards.

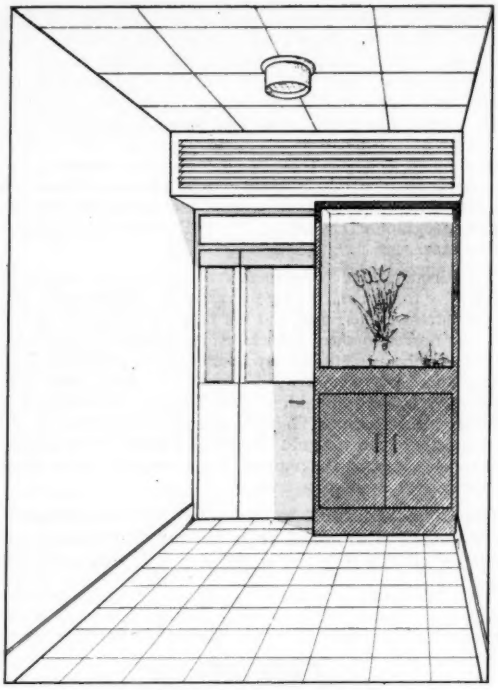


Fig. 3—View from the bed.

that, where patients have private rooms, it is important to provide a dayroom where the convalescent can sit and talk to others. Such a room, with amenities such as television, can be a useful incentive for the "ill" to get out of bed as soon as possible—e.g., after operation. But the advantages of social life can be secured without the disadvantages of the open ward.

An attempt to combine the two is the *cubicle*, which gives the patient a certain amount of visual privacy by surrounding his bed with movable curtains. Welcomed by nearly all, this plan has had a long trial but, though it is socially desirable it has proved medically disastrous. The curtains hamper medical ministration to the patient, and if infection occurs they harbour and disseminate it. The cubicle has been tried and has failed. The proper alternative, on which we should now embark, is the conversion of public wards into private wards. Not only would this reduce the risks and discomfort for patients but it would remove the present mental barrier between the public and private ward, giving the ordinary patient the benefits that the well-to-do now buy privately. It would be an advance in accordance with the wishes—conscious and unconscious—of the present generation.

I shall now explain one way in which it could be done.

THE CONVERSION

Any ward in any hospital, provided it is at least 28 ft. wide and has adequate outside windows, can be converted into a series of private wards with a central silent service corridor (fig. 1). If the ward is less than 28 ft.wide, one side of it can be converted to private wards for the most ill, while the other can be left open for the active and the convalescent.

Judging by nursing and medical experience, the private ward should be at least 8 ft. wide and 11 ft. long (10 ft. is the very minimum). If the height of the existing ward seems too high for the private ward, a false ceiling can be put in, provided it does not interfere with lighting. Fig. 2 shows how such a room might look.

The walls should be made of modern materials, in pastel colours, without angles and crevices. They should withstand washing-down with a powerful hose or preferably a steam jet. The wall of the ward which separates it from the corridor is the most difficult to sterilise. It contains a door, which must be wide enough (4 ft.) to permit the entry and exit of a "loaded bed". The remaining 4 ft. should include, I suggest, an inset cupboard for clothes and personal belongings (fig. 3). This could be 4 ft. high, 4 ft. wide, and 1 ft. deep, and would project into the private ward. Such a cupboard not only would be convenient—at present the patient's relatives often have to take his clothes home because there is no place for them in the ward—but also would help the patient's morale. To deprive patients of their own apparel and possessions on admission to hospital is to inflict unnecessary trauma on the many who need to retain some contact with familiar things, and who want to feel sure that they are going out again.

The principal question to be answered, however, is whether we can combine the advantages of quiet and visual privacy with efficiency of medical care and safety for the patient. To this end I propose that the door should have a tempered glass panel inset 4 ft. above ground level. Above the cupboard will be a second glass panel, with or without glass sides. Through these windows light will reach the service corridor, and the patient can be seen by the doctors and nurses. They should be fitted with quick-release blinds which can be pulled down for social and medical reasons.

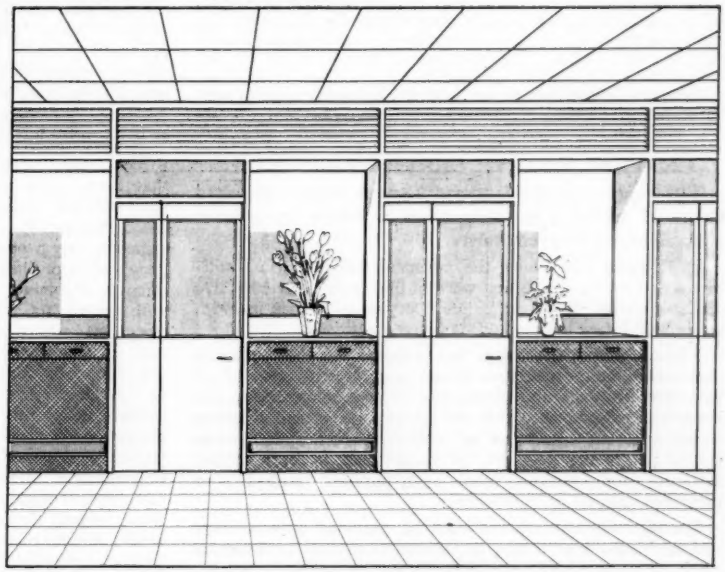


Fig. 4—View from silent corridor.

As fig. 4 shows, there will then be a shelf, accessible only from the corridor, above the cupboard. On this shelf, visible to the patient through the glass panel, the patient's flowers can stand. They can be arranged and tended without coming into the room, and they will decorate the service corridor too.

The top of the cupboard has a shallow drawer containing the patient's notes, charts, &c. This can be pulled out either into the corridor or into the ward. At the base of the cupboard a strip light illuminates at night the floor of the corridor.

The corridor must be at least 6 ft. wide—so that a bed can be wheeled out of the ward and turned into it. At the end the nurses should have a small room with an observation panel enabling them to see down the corridor. This room would have a panel system of lights for communicating with each private ward. A wish for a nurse would be expressed by a light on the door of the private ward door and a corresponding warning light on the nurses' panel.

Conversion of open wards into private wards in this manner would inevitably means some loss of beds—averaging perhaps 10%. This, however, would be offset by the lessened wastage from sepsis and consequently improved bed occupancy. The actual reduction in annual turnover might in fact prove negligible.

The financial cost of conversion would not be high if pre-manufactured units on a large scale were used. These could be made adaptable to open wards of considerable variety.

CONCLUSIONS

The open ward is an anachronism. It should be converted into a series of private wards.

In a private ward the patient is less disturbed by noise and lights and the vicissitudes of fellow patients. He and his visiting relatives have privacy, and both investigation and treatment are facilitated. Above all, an infected patient can be segregated from admission till discharge, and his room can be sterilised when he leaves.

My thanks are due to the architects, Messrs. Easton & Robertson, and in particular to Mr. S. E. T. Cusdin and Mr. J. Burden, for translating my ideas into practicable plans. I am most grateful to my wife for helpful advice. The drawings to my design are by Mr. A. Rudenski.

This paper is sponsored by the Vaughan Hudson Clinical Research Trust.

CENTRAL HEALTH SERVICES COUNCIL

THE report for 1959 of the Central Health Services Council [1] includes a summary of a report by a joint subcommittee on prematurity.

In England and Wales the perinatal mortality (i.e., stillbirths and deaths in the first week of life) is 35·1 per 1000 live and still births. If it were 28 per 1000, as in Sweden in 1955, some 5000 infant lives would be saved every year.

The subcommittee remarks that in prevention good antenatal care including the necessary blood-tests, careful selection of cases for hospital confinement, and an adequate number and ready use of antenatal beds are all important; and it draws attention to the advantages of combining the hospital care of premature infants with that of mature sick newborn infants suffering, for example, from birth injuries, asphyxia, or hæmolytic disease of the newborn.

Special baby-care units should be provided only in large and medium-size maternity departments catering for abnormal obstetrics, and these hospitals should have enough antenatal beds as well as emergency beds reserved for unbooked cases of labour. These special centres would accept patients in premature labour, and premature and other infants from the district and from smaller maternity departments within a defined area. For every 1000 total hospital and domiciliary live births, at least 6 cots for premature and other sick newborn infants on an average of five weeks' stay are recommended. For convenience of administration each unit would have not less than 20 cots (enough to serve a population of 200,000), though geographic circumstances will sometimes justify a smaller unit.

The subcommittee recommends that each unit should be directed by the consultant pædiatrician, in collaboration with the consultant obstetrician and his team, and should have at least two nurses to three babies. An emergency resuscitation team should be available at any hour for emergencies in other hospitals or in the home. All women in labour before the thirty-seventh week should, if time permits, be admitted to the area special centre. The subcommittee recommends that the premature infant should not be discharged from hospital until it is known that the home circumstances are suitable and any necessary help is to be had.

The Council decided to set up two new committees—one to review operational research into prescribing, and the other to examine the scope and methods of health education.

1. Central Health Services Council: report for the year ended Dec. 31, 1959. H.M. Stationery Office. 1960. Pp. 24. 1s. 6d.

Parliament

Wolfenden Part II

THOUGH the Government acted swiftly on the part of the Wolfenden report which dealt with prostitution, they have made no attempt to introduce legislation to carry out the Committee's recommendations on homosexuality. On June 29 Mr. KENNETH ROBINSON called on them to take early action because the topic was important, not only to the minority directly affected by the law, but also to the rest of the community. The incidence of homosexuality was not easy to determine, but the best estimates were that in Britain today about 1 male in 20–25 was an active homosexual. They were not confined to any particular social class or professional group. There was no evidence that homosexuality had increased recently or was increasing. Homosexuality was seldom a matter of choice for the individual. According to the generally accepted view among doctors and sociologists it was a disability—a deviation from the norm of the same sort of order as left-handedness or colour-blindness.

The chief recommendation in the Wolfenden report was that homosexual acts committed in private by consenting adults should no longer constitute a criminal offence and it placed the age of consent at 21 in this connection. Far from removing any protection from the young that the existing law provided, it recommended increased penalties for some sexual offences involving young persons. Interference by the law with private acts of adults could be justified only on exceptional grounds of public interest. He did not consider that such grounds existed in this case. Nor did he think that there was equity or consistency in the administration of the law. It was largely the individual attitude of chief constables to homosexuality that determined how zealously, or otherwise, the police in a given area pursued it. The present law also gave unparalleled opportunities for blackmail. Many of the most objectionable features of homosexuality stemmed directly from the criminal stigma that attached to it. It was often said that if we relaxed the law relating to private acts, homosexuality would spread, homosexuals would feel free to proselytise, and young people would be endangered. Nothing of the kind had happened in countries which had relaxed their law, and all the

evidence suggested that the people who normally engaged in homosexual acts between adults were not the same people who tended to seduce young persons. It was also said that to change the law would be to appear, at any rate, to condone and encourage homosexuality. Did we condone and encourage adultery or Lesbianism simply because we had failed to make either a criminal offence?

But the main argument adduced against reform was that public opinion was opposed to it, or was not ready for it. Did that mean that we could never change the law until an overwhelming majority of the people demanded that change? If that criterion had been adopted in the past, we should still be hanging men for stealing sheep, and chaining lunatics on beds of straw. In difficult questions like this, what sort of opinion should the Government consult before acting? He suggested that it should be the opinion of a reasonable cross-section of the community which had taken the trouble to study the matter intelligently and objectively—and there was no doubt where such opinion lay in this matter. For a Government which wanted to make this change, there was ample and demonstrable public support to justify their action.

Mr. W. F. DEEDES admitted that since he had been obliged to get to grips with the subject he had partly changed his mind. He could no longer accept the present law as the last word. Surely the issue now was not so much whether there was to be a change, but how and when—particularly when. It was not difficult to reach a satisfactory intellectual answer to this problem. It was more difficult to face the administrative consequences of any change. The more the subject was debated the more likely the public was to see the force of the main Wolfenden recommendations, but he thought that there would always remain an adamant minority, and perhaps a majority, opposed to a change. Three essential preliminaries to change were a programme of research; further discussion and debate, however interminable, to help public opinion to come to grips with the subject; and more evidence that those who saw with such clarity the distinction between crime and sin in respect of this offence were sharing that doctrine with a wider audience and fortifying it for a change in the law.

Though Dr. A. D. D. BROUGHTON sympathised with homosexuals as individuals, he thought that we must legislate for the good of the community as a whole even if by so doing it hurt a minority. Homosexuality occurred in all personality types, but two types ought to be mentioned. The first was the adolescent and mentally immature adult, some of whom overcompensated for their inferiority by bravado. They were aggressive types, apt to be bullies, and as homosexuals they were dangerous. The present laws kept that type under control to a large extent. The second personality type was the severely damaged personality. Some were obviously effeminate, flauntingly exhibitionist, and deeply resentful and anti-social. Given a change in the law, he believed that those two types would snap their fingers in the face of public opinion. We might expect to find a display in public of homosexual feelings, particularly by the exhibitionist types. He feared that bullies and seducers in positions of authority might make homosexual demands on their subordinates. It would be a thoroughly bad influence on the young in the difficult period of their transition to heterosexuality. The law at present might be too savage in some cases, but he believed that homosexual practice should remain an offence to show our disapproval of that type of conduct.

Mr. WILLIAM SHEPHERD opposed the motion, but he pointed out that both sides had much common ground, particularly the need for more research. He would like to see a United Nations organisation spending a great deal of money on a comprehensive investigation. There was also need for a more liberal interpretation of the existing law. His own feeling was that justice was done in these sorts of circumstances by having a deterrent law liberally administered. As Mr. Shepherd saw it, the homosexual fixed his resentment of heterosexual society on the existing law. But what the homosexual really wanted was not a change in the law; he wanted to bring about a condition in which he was no longer in a minority. He tried to rationalise this in terms of objection to the law. Though there might be some marginal advantage to homosexuals in an alteration of the law, it would not on the whole change the attitude of society to homosexual practices. Therefore, there would be no real advantage to the average homosexual. Nor must we forget that there was a wide variety of homosexual and heterosexual tendencies. We were not dealing with a helpless minority who had only one choice before them.

Though we had sympathy for homosexuals, they were not the most desirable section of our community. They were terribly promiscuous, and a damaging aspect of this promiscuity was that the homosexual was a proselytiser. A recent report on 127 homosexuals [1] showed that 24% would be prepared to engage, in some circumstances, in homosexual activities with boys. He suggested that a relatively small amendment in the present law, though it would not meet the total demands of the homosexuals, might go some way to putting the position on a more equitable basis. If the relevant section of the Act of 1885 was annulled, acts of gross indecency among consenting adult males in private would no longer incur the penalty of the law; but acts of sodomy would. Heterosexual acts of sodomy also incurred the penalty; therefore homosexuals would not be able to say that they had been singled out.

Mr. R. A. BUTLER, the Home Secretary, said that though progress had been made since the debate in 1958, there were still great differences of opinion. In the last debate it had been said that we might get the best of both worlds by keeping the law as it was but narrowly limiting its enforcement. It had been suggested that prosecutions should be instituted only by the Director of Public Prosecutions, with the consent of the Attorney-General, and taken only if the public interest so required. But local administration of criminal justice through chief officers of police and the right of the private citizen to prosecute were essential features of the legal system of England and Wales. Mr. Butler considered that a very special case must be made out before the prosecution of any particular offence was reserved to the Director of Public Prosecutions. It was difficult because there was also an objection of principle. It would mean either that enforcement of the law against a particular class of offender, such as consenting adults committing homosexual acts in private, would cease, or that some limited class of offender would be singled out by some discretionary process for prosecution, and all others would be allowed to break the law with impunity. It would also raise practical problems.

For example, who would assess the public interest? What did "consenting" mean? Why, for a man, should the age of consent be 21, while for a girl, in certain Acts, it was 16? The Wolfenden Committee excluded the Armed Forces; were we to accept its recommendations to that extent? How should we define the words "in private"?

He accepted the need for three preliminaries before action—research, education of public opinion, and that reformers should admit that homosexuality was, in general, an undesirable practice. He could report some progress in research:

A project under the auspices of Birkbeck College was being financially supported by the Home Office. Its object was to compare the psychological and other characteristics of homosexuals sampled from different groups, and to investigate whether those characteristics differed from group to group or differed from characteristics of non-homosexuals. This involves a study of family and social, educational, and occupational, background, and the personal characteristics of homosexuals who had been convicted of such offences or had been treated in clinics because of such tendencies. A second line of inquiry was a study of groups and the way in which homosexuals associated with them, with particular references to the means by which and the extent to which homosexual conduct spread within society. Some investigations into the possibility of influencing homosexual behaviour by psychotherapy or medical means, such as

1. Westwood, G. A Minority. London, 1960.

the use of œstrogen, were being made by the Prison Medical Services. It was not possible yet to draw any firm conclusions.

A fundamental question to which we were always brought back, Mr. Butler continued, was the existence of people to whom criminal law and moral law were coterminous. They considered that if conduct was not prohibited by criminal law, there was no reason why they should not indulge in it. The restraints which criminal law imposed, therefore, still remained important. In a period when religious and ethical restraints were weak those of the criminal law acquired a special significance. He would not regard this as being a time to let down our first line of defence, unless he found an absolutely satisfactory way of doing so.

During this period of research and consideration, we must ask ourselves whether the removal of the legal sanction against homosexual conduct between consenting adults in private would weaken the moral sanction against homosexual conduct. Would the removal of the legal sanction make it more difficult or less for the bisexual and the young to resist temptation to homosexual conduct? Would homosexuals be more ready, or less, to break their homosexual associations and to seek medical treatment? Would homosexual conduct spread, or, losing the glamour of its rebellion, would it decline? The answers to those questions would become less speculative as our knowledge grew. Our judgment was likely to be sounder, not if we shunned discussion but if we allowed discussion to proceed, if we examined every concrete suggestion made. He recognised that the present law imposed hardship on the constitutional homosexual and that it had its own undesirable consequences. He did not believe that the full case for a change had yet been made, nor was he convinced that we were yet in a position to take a final decision on what the precise nature of the change should be. We needed more information and we were trying to get it. We needed more time to discuss the fundamental issues of the relationship between law and morals and more time to weigh the possible, and necessarily speculative, consequences of modifying that relationship.

The motion was lost by 99 votes to 213.

Professions Supplementary to Medicine Bill

At the committee stage of this Bill in the House of Lords on June 28, Lord ST. OSWALD said that during the long discussions which preceded its preparation, great importance was attached to the principle that there should be numerical equality between the representative and medical members of the new Council. It had always been assumed that the representatives appointed by the English Colleges, the Scottish Corporations, and the General Medical Council would in fact be registered medical practitioners, and the point was therefore not specifically dealt with in the Bill. Amendments to place the matter beyond any possible doubt had been put down by Lord Cohen of Birkenhead. He later withdrew them, but the Government had now put down amendments in similar terms, since it seemed that they might improve the Bill.

As at present drafted, the Bill provided for the great majority of the medical members of Boards to be nominated by the English Royal Colleges and the Scottish Corporations. This was in accordance with the scheme negotiated with representatives of the supplementary professions and the Joint Consultants Committee. The Bill was silent as to the procedure to be followed by the medical bodies in making nominations. At the second reading, Lord Taylor had asked whether on the radiographers' board it would not be possible to guarantee the representation of at least one therapeutic radiologist and one diagnostic radiologist. The Government was therefore introducing an amendment, not restricted to the radiographers' board but applying to all boards to be created, to ensure that before nominating any person for membership the English Colleges and Scottish Corporations should consult such specialised medical bodies as they considered appropriate. They had preferred this wider method of dealing with the problem because other consultants had a special interest in the work of particular boards—for instance consultants in physical medicine and orthopædic surgeons in the physiotherapists' board, the occupational therapists' board, the remedial gymnasts' board, and pathologists in the medical laboratory technicians' board. It was clearly desirable that, when making nominations the English Colleges and Scottish Corporations should not overlook the desirability of prior consultation with any specialist professional body which seemed to them to have a particular interest in that particular field. It had, however, always been assumed that the Colleges and Corporations would, in fact, carry out consultation of this sort. The Government were sure that this assumption was correct, but since they were conscious of the importance of making entirely sure that specialist professional opinion was not overlooked, they now put forward an amendment specifically designed to secure it. While ensuring this important object the amendment preserved the principle that ultimate responsibility for making the nominations should be in the hands of the English Colleges and Scottish Corporations.

Viscount KILMUIR, the Lord Chancellor, moved an amendment restoring to the Bill the express powers for parties to proceedings before a disciplinary committee to obtain writs of subpœna in whatever part of the United Kingdom the committee may be sitting.

Industrial Dermatitis

On the adjournment on July 1 Dr. BARNETT STROSS said that there was widespread anxiety among workers because they felt that often a diagnosis of industrial dermatitis was relinquished by the medical boards some time after injury payments had been made. The diagnosis was then changed to dermatitis due to constitutional causes and injury payment ceased. An appreciable percentage of recrudescences were diagnosed as being constitutional in origin though payment had been made in the first instance. Medical knowledge on the issue was not an exact science. There were real divergencies of opinion both as to diagnosis and prognosis. Because variations militated against the workers and created confusion, he felt it right to raise the matter in the House. He did not think we ever would know more about the problem until industrial dermatitis was scheduled as a notifiable disease. He asked the Minister whether he could use any method to point out to the medical profession that it was no part of their duty to refuse the benefit of the doubt to the worker because they feared that he might not recover so quickly if he were certified.

Mr. W. M. F. VANE, joint parliamentary secretary to the Ministry of Pensions and National Insurance, pointed out that under the National Insurance (Industrial Injuries) Act, Parliament laid the responsibility for diagnosis and assessment in these cases on the independent adjudicating authorities. The medical members of the medical appeal tribunals were consultants of high standing in their profession, nominated by the universities. It was reasonable to suppose that their views in general reflected orthodox medical views. 'There was no such thing as a departmental line with regard to dermatitis. These decisions were not taken hastily. In difficult cases, a man or woman might be seen by as many as five independent doctors, of whom two were consultant dermatologists. There was proper machinery and a well-known line of appeal to the medical appeal tribunal where, in dermatitis cases, one of the members would always be a dermatologist.

QUESTION TIME

Waiting-lists for Mental Deficiency Hospitals

The number of staffed beds allocated in England and Wales to mental deficiency at the end of 1959 was 58,904 (56,066 in 1956). The waiting-list was 5918 (6247 in 1956).

In England Now

A Running Commentary by Peripatetic Correspondents

I've had a glimpse, or little close-up, of telly-pillory. "There", they said, "sits Rhadamanthus, who runs that programme *Fiat Nox*—you must know it". I mumbled a negative. "He wants to collect the platform speakers and one or two from the floor after the debate just to . . . I hope you can." It could not have been less convenient, but if the others were playing I supposed I was. So, after the debate, I was whisked away to a grand but remote hotel to find my fellow debaters sipping tea. "He would like to take you first", said a staff-captain and leaving the untasted cup to cool I walked with firm steps to the chair.

The lights shone warm. They opened and shut a wooden clapper-thing under my nose. Someone said "knit one, purl two" to someone else and Rhadamanthus began his soul-search. He searched for some time—some say five minutes or more. I said, not aloud "I will take heed unto my ways, that I offend not with my tongue", spoke up for the faith that was in me, and disagreed firmly but ever so gently with Rhad. We closed on a quiet note; those following registered kind approval; I heard the next go through with it and took my leave.

"How queer", I thought at intervals in the next two days, "that my face and voice will appear, sudden and unannounced, before many that know them and utter words, acceptable or unacceptable, on matters of some moment. How queer that I shall reveal my thoughts to an unknown host; that, to some small extent, I have been speaking publicly for my profession. How queer. I wonder just what I did really say". I need not have troubled. Rhad, or someone, sent me down into silence, a goat, not a sheep, and at least two of my fellows with me. So I've stopped wondering those things, and wonder instead whose, really, were the velvet-padded claws that for an hour or so held us, played with us, observed our reactions, and tossed us away. The power of Rhadamanthus is deputed power; what is its *fons et origo?* Is it a machine out of control, like those the Erewhonians destroyed? Is it a corporation (in which case not much better than a Ministry), or were we in the casual clutch of Demos itself?

* * *

My visit to Town happened to coincide with the summer show of the National Rose Society. The displays of the professionals were so massive that they battered the senses and some of their impact was lost. Comparatively few varieties were shown in this section—most of them recently introduced blooms displayed as a sort of hit parade.

The amateur section had more variety, and here one saw old favourites holding their own with the novelties. Among the named varieties Medicine had not been entirely forgotten, and I was pleased to see *William Harvey* and *Dr. F. G. Chandler*. On the other hand, that vulgar rose *The Doctor* was conspicuous by its absence. Names of blooms are always interesting and may show some deep psychological motivation. The pinks and whites are usually feminine, solid downright reds and crimsons tend to be masculine, while the salmons can scarcely be said to have found themselves. Yellows are largely descriptive in name, or may even be abstract. Of these the most ubiquitous, most handsome, and the biggest prize-winner seemed to have a special symbolism. It was—yes—*Peace*.

* * *

Florrie was admitted at 1 A.M. and managed to persuade both housemen and registrar that she needed a consultant's opinion immediately. For several weeks she occupied a hospital bed and did her best to convince us that she was totally paralysed. She was, however, capable of vigorous movement in order to resist anyone's attempt to examine her. She was also resistant to all forms of treatment, both physical and psychological.

We were in the middle of a ward round. I was wondering how much longer Florrie could go on occupying an acute medical bed. The psychiatrists, having sweated blood and tears over her for years, weren't frightfully keen to take her over. Suddenly, ignoring the notice on the door and Sister's vociferous remonstrations, Florrie's sister dashed into the ward shouting, "Florrie, Florrie, you've won the pools. Seventy-five thousand pounds. Get up, Florrie. You must get up." And Florrie did get up, instantly and unhesitatingly. To the astonishment of the other patients she threw off the bedclothes, and ran out in her hospital nightie. I was witness to the fact that her limbs moved faultlessly. What I did not see was the hired Rolls Royce waiting for her at the hospital gate and the porter on duty so astonished that it never occurred to him to try to stop her.

We haven't seen Florrie since, though we did see her photograph in the newspaper, looking very gay in a posh London hotel. A week later the hospital nightgown—which she wore for her abrupt departure—was returned, addressed to me, wrapped in expensive paper and tied with pink ribbon. I suppose one is lucky if, once in a lifetime, one witnesses the cure of a disabling and chronic condition. I should like to repeat the experiment with several other cases, but I fear that it may be difficult to provide the appropriate circumstances.

* * *

It is not true that the Russians have not got modern hospitals, though the hospitals where they keep patients may give this impression. We had been shown round the Second Medical Institute in Moscow. We compared it with the hospitals we knew in Britain. On the whole it was favourable. The wards were a little overcrowded and not nearly as fanatically tidy as ours, but they looked more homely. Patients and relatives were talking in the corridors. Everywhere were tall green potted-palms devoid of any kind of charm. Obviously the last 5-year plan had left the health service as far from Utopia as us.

After two weeks in the country we were beginning to understand the secretive Slav mind. We must approach the answer backwards. In which of the large public buildings in Moscow are you least likely to find a hospital? The University? No—might easily be one there. The Ukraine Hotel—four-starred on the American's travelling Gunther? No—the British Embassy lodges here. Nothing could get past Carleton Brown's eager eye. Could it be in Lenin Stadium—Moscow's White City? Yes! With devilish cunning, hidden among the palatial washrooms of the Heroes of Sport was a magnificently equipped hospital—all the better for the dearth of Heroes of Sport hors de combat—and six laboratories run by professors using secret East German, Czechoslovakian, Russian machines (code name E.E.G.) for their research. Here thirty full-time doctors, specialists in E.N.T., ophthalmology, gynæcology, and dentistry worked in wide rooms with all the new machines they could desire.

It was all very impressive and just what we had hoped for. We have a lot to learn from the far-seeing Russians. There will always be jobs for the boys looking after superbly healthy people.

* * *

If the Sunday papers continue to grow, I shall have to stop taking them, or get up earlier on Sunday mornings. A minor reason for this painful decision will be the fact that the day is already barely long enough to finish the news; but the most important reason is different. Our newsboy can no longer push the papers through our minute letterbox, and they stick out blatantly until late in the morning, when I creep shaggy-haired downstairs to rescue them. I am getting tired of the reproachful glances of churchgoers and self-righteous car-cleaners as I slip my hand round the door to drag the papers out, or, still worse, have to go right outside to haul them out of the corner of the box where they usually stick. I suppose a third alternative would be to get a larger letterbox.

* * *

Glory be to God for dappled things
For cheques of double value that Sir Harry brings.

Letters to the Editor

ABDOMINAL DECOMPRESSION IN LABOUR

SIR,—It was indeed gratifying to find in *The Lancet* of May 28 a paper on abdominal decompression in labour from so distinguished a school as Edinburgh. It was encouraging to learn that Dr. Scott and Dr. Loudon had achieved very pleasing results considering the experimental conditions under which they worked.

Perhaps you would allow me some space in your journal with a view to aiding progress. We have done a great deal of laboratory work and have tried a large number of modifications on the drawing-board, in apparatus, and in technique.

One of our pumps, the Hoover Constellation, gives a 77 mm. Hg drop of pressure continuously, can reach 100, and with a small modification will exceed 110 and is then ideal. Coupling tube of ample cross-section or bore is essential, as is an adequate thumb control to re-establish atmospheric pressure. In my experience thick-walled pressure tubing causes so much turbulence that gauge readings of pressure are worthless. The elementary matter of reading the true pressure under the cage or upon the abdomen is something which we can guarantee to be reliable. As a subject I am familiar with pressures down to 200 mm. Hg below atmospheric but as an observer with pressures to 300 mm. below.

At about three-quarters dilatation of the os most patients drop the pressure by 75 mm. and gradually work to 100. When we used a cage like that of Dr. Scott and Dr. Loudon—i.e., without a backing plate—many primigravidæ used a pressure drop of 125 mm. Our record patient achieved a drop of 300 mm. I personally tested a parturient at the time in a polyvinylchloride suit $^{4}/_{1000}$ in. thick. It lasted for 25 minutes of labour when holes developed in the material. It was then decided that we should use nothing thinner than $^{6}/_{1000}$ in. P.V.C. It is a matter of experience that thin material is better to work with than thick, mainly because of clinging and consequent sealing. We are well aware of the advantages that result from pressures lowered 50 mm., but we strongly recommend the full use of further decompression when the patient demands it. Rapidity of decompression is not only essential but patients used to cry for it. However, we are now able to obtain effective pressure in 6 seconds. Last week we had an experience that reflects the value of pressures beyond a 40 mm. drop. While occupied with our own "decompression" patients, we were called to a parturient who was suffering acutely in spite of having had pethidine. For a patient who had never even seen our device it was remarkable that she lowered the pressure 75 mm. at her very first run and at the same time expressed her satisfaction.

We repeated our previous experience with 200-gauge polyethylene, but under critical conditions and with equipment like that used in Edinburgh. The bag always burst at the first run, sometimes at a reduction of 80 mm. and at others of 100 mm. In parturients the bag held for only a few contractions at the pressures in routine use. The preference for a bag that does not enclose the lower extremities was surprising having regard to the fact that our climate is warmer than that of Edinburgh. We have very rarely had complaints about perspiration, which, however, can be considerable when the subject is nervous. It is not very wise to save the legs from pressure when the breasts are squashed as flat as those in the illustrations. I have always objected to the constriction of the knickers above the knees: if pooling of blood occurs in the legs, the fœtus as well as the mother will suffer. The knickers used are of course exhausted more readily than the full-length suit. We sincerely believe that the suit should be opaque, attractive, strong, and full length.

We have substantial evidence that the pain of labour is neither an intrinsic visceral pain nor referred, but that it is based on a reflex causing painful spasm of the sacrospinalis muscle posteriorly and the rectus anteriorly. Abdominal decompression lengthens or stretches the sacrospinalis, which soon shortens pari passu with lordosis. A full effect results only when the cage covers all of the epigastrium, this ensuring what amounts to a very deep inspiration. The Edinburgh cage fails in this respect.

A recent visitor from Edinburgh was astonished at the ease with which an obstetrician and an operative managed a number of women simultaneously. Thus he saw, within an hour, the fifth batch of three pregnant women and two parturients having their appropriate decompression. It has been found that a few runs of decompression after the 38th week produce such preparation of the birth canal that the first stage is shortened even more than we reported last year.

Medical School,
University of the Witwatersrand,
Johannesburg. O. S. HEYNS.

SHORTAGE OF RADIOGRAPHERS

SIR,—Your annotation of June 11 again drew attention to the shortage of radiographers. With adequate publicity the shortage could easily be overcome. Too little is known about radiography among potential recruits. None of our radiographers had heard of radiography at school, and all were agreed that if there were more lecturing on this career at schools it was likely that recruits would come forward. At this hospital there is no school of radiography, but lectures have been given at a few girls' schools as an experiment.

The lecture was offered to 13 schools: 7 refused and 6 accepted. At one school the lecturer was invited to lecture again later to a more junior group. The lecturer used slides, colour slides made to illustrate radiography in the X-ray department, a ward, and the operating-theatre, and work in the dark-room, and slides showing the radiographs obtained.

Interested girls were invited to visit our department in small parties. When the girls came they were put into white coats and distributed round the radiographic rooms and the dark-room, saw a barium meal in progress, were shown a collection of radiographs, and were taken round a ward. The results of two lectures given to girls about to take the O level G.C.E. are not yet available. After the other five lectures, ten girls have applied to, and have been accepted at, schools of radiography, an average of two per lecture. This result cannot have been influenced by the recent salary increase, for the first eight recruits made their decision before the salary increase was announced. The latest published figure of radiography training posts [1] was 767, of which 132 were unfilled, though the position is even worse than this figure would suggest, for a number of those in training are from overseas and will be returning home on qualification. At the same rate of recruitment only sixty lectures would be needed to fill all existing training vacancies in the country.

The following remarks by headmistresses concerned are relevant:

"I agree that this is a training about which girls seem to hear very little." "I am quite sure that if more people knew about little-publicised careers any shortage would be quickly overcome." "A difficulty for some girls who might do radiography is how to spend the year between passing the O level G.C.E. at 17 and starting radiography at 18." "To attract girls of this age the lecturer should be young."

The age and personality of the lecturer are obviously important. A senior member of the staff of B.B.C. television whom I was trying to persuade, so far unsuccessfully, to interview a radiographer on her programme for publicity, said that to appeal to schoolgirls the radiographer interviewed should be "young, warm, and vital". Our lecturer, one of our senior radiographers, is a young woman in the twenties. An important point which emerged was that many girls in the sixth forms after passing the O level G.C.E. have already decided on a career. The audience must include those about to take this examination.

1. *Radiography*, suppl. June, 1960.

The importance of publicity is stressed in the reports of the Ministry of Health study group [2] and the Faculty of Radiologists.[3] Its possibilities were shown three years ago by the effect of a five-minute talk on Woman's Hour, after which there were many inquiries at the Society of Radiographers referring to the broadcast. There have been some demonstrations at careers exhibitions and some lectures at schools, but not nearly enough. Other professions with a similar problem have been more enterprising. An A.T.S. officer I used to know—"young, warm, and vital"—lectured at schools for months on end to encourage recruitment. One of our radiographers heard this lecture at school and after hearing it several girls joined the A.T.S., but there was no lecture at this school on radiography. The British Orthoptic Board, to facilitate recruitment, have had made a twenty-minute film with a sound track, showing the training and work of an orthoptist, which has been shown at schools, at careers exhibitions, and at other meetings which headmistresses have attended.

I do not agree with the statement in your annotation that it is vital for men to take up radiography. We much appreciate the first-class male radiographers already in the hospital service, but many of our best departments are run by women, enough women remain in the profession to fill the senior posts, the salary is not going to be large enough for a man with family commitments, and for this reason alone men should be discouraged from applying for training.

We have suffered long enough from the radiographer shortage. The present trainee vacancies and vacancies at the additional schools needed could be easily filled by intensive lecturing at girls' schools by a team of selected young radiographers with slides or a film, the lectures being followed by visits to X-ray departments, and by allowing students to start at 17 and to qualify at 19. Regular B.B.C. sound and television programmes would help. Someone must initiate this programme. The Faculty of Radiologists has produced a comprehensive report. Will it act?

I am much indebted to Mrs. B.-W. Hughes, our lecturer, for her willing and effective cooperation, to Miss K. R. Askwith, our superintendent radiographer, for much trouble taken over the reception of the visiting schoolgirls and during the making of the slides, and to Mr. Esmond Wilson, director of the Royal Society of Medicine photographic unit, for the slides.

Whittington Hospital,
London, N.19. G. OSBORNE.

TOO MANY CALORIES

SIR,—I read your leading article of June 11 on obesity with interest: it is a problem, personal or professional, to many of us.

One can regard obesity as a failure of that marvellous regulatory mechanism, appetite. It is one of the miracles of life that some of us eat exactly as much as we metabolise—one slice of bread a day in excess and weight would be soon piling up. What makes these people refuse that extra slice of bread? Conversely, what keeps their less fortunate fellow men still hungry after they satisfied their "caloric requirements"? Overweight may be due to overeating (in my opinion this tired observation is a tautology, devoid of meaning) but to many of our patients, and some of their doctors, normal weight seems to be the uncertain reward of prolonged semi-starvation. Let such a person "forget himself" over a long holiday weekend and up goes his weight. To some of the victims the cure appears worse than the disease.

Much remains to be learned about metabolism and eating habits, and the differences between overweight people and other "big eaters" who do not gain weight. In clinical medicine the air needs to be cleared of countless claims for a cure for obesity. Did the results last? As in cancer therapy we ought to demand to see the proportion of "three-year cures" and "five-year cures". A method that might work well but patients don't accept it is not a good method. Slimmed-down obese patients who regain their former weight as soon as they are lost to strict supervision were helped no more than alcoholics who return to drinking as soon as they are released from an institution.

Does anyone know of claims for long-term results in the treatment of the obese in a meaningfully large number of patients?

San Francisco. STEVEN E. ROSS.

A CHLOROFORM SYNDROME?

SIR,—Dr. Latta (June 25) describes a "chloroform syndrome". It seems strange that in this day and age anybody could have "continued observation" of someone exposed to repeated inhalations of this very powerful poison. Everybody should know that not only has chloroform caused ventricular fibrillation but also primary cardiac failure in quite lightly anæsthetised patients and extensive liver damage which has proved fatal. Surely no-one would prescribe daily or tri-weekly inhalations of chloroform for any therapeutic purpose, and if a patient was addicted to this drug surely immediate steps should be taken to remove the supply. The fact that the patient is active at all is far more amazing than the presence of a "chloroform syndrome", which one would have thought was inevitable.

London, W.2. MARGARET JOAD.

THE FEMALE PROSTATE

SIR,—Mr. Thomas Moore's erudite contribution (June 18) on the female prostate draws attention to dysuria in women due to constriction at the bladder neck. His article is of great importance because these cases are not rare and the condition causes both mental and physical distress. It is usually misdiagnosed as having a gynæcological cause but the treatment by the gynæcologist invariably intensifies the misery of chronic urinary retention and increases the dangers of the concomitant evils.

It is difficult to be sure that such constriction of the urethra is due to the female prostate. Comparison with the male condition is circumstantial. The bewildering conglomeration of glandular tissue round the female urethra is not at any point recognisably prostatic, or even elementarily prostatic, under the microscope. The female animal in which periurethral tissue most closely approximates to the histological appearance of the prostate is the multimammate mouse (*Mastomys erythroleucus*, Temm). This was investigated by Brambell[1] who told me that even in these animals it is extremely difficult to be sure that the condensation of cells round the female urethra is of prostatic origin. Again, prostatic carcinoma in the female is unknown in the animal kingdom.

Yet it is important, in considering treatment, to decide whether constriction of the female bladder neck is prostatic because, if it is, then Moore's treatment is logical. If, however, as I believe, there is no prostatic tissue, either formed or rudimentary, to be recognised round any female urethra, then resection of the mucosa of the female bladder neck, and presumably the immediate underlying tissue, is not logical though it may be effective.

But it certainly is not necessary, because a cure can be obtained rapidly by safer and simpler means since these unfortunate women, even after the attentions of the gynæcologist, respond to dilatation of the urethra and bladder neck, up to the size of the little finger according to the amount of resistance encountered. This can gently be done with Hegar's.

There are no complications to this treatment and the symptoms improve rapidly after the first dilatation. It may

2. *Radiography*, October, 1959. Report of Ministry of Health Study Group.
3. The Shortage of Radiographers: report of The Faculty of Radiologists, 1959.

1. Brambell, Davis. *J. Anat.* 1940, **75**.

have to be repeated more than once at monthly intervals, but it will eventually give permanent benefit and then the urine, if infected at the onset, will be found to be sterile.

Indeed, it may be that the effective part of Moore's treatment is not the loop-resection but the dilatation that the resecting instrument unavoidably causes.

I congratulate him on drawing attention to this obscure but common cause of female discomfort.

London, W.1. W. SKYRME REES.

SUPERDOSAGE CHEMOTHERAPY OF MALIGNANT DISEASE

SIR,—We should like to draw the attention of Dr. Freedman and Dr. Davidson (June 25) to the considerable literature concerning the use of intramedullary injections for the purpose of venography [1] and the possible dangers of such injections.[2] It would seem likely, therefore, that the injected marrow would merely pass into the occluded venous system. We would suggest, for their consideration, that the marrow-cell suspension be kept in a suitable medium at room temperature,[3] or even better, at 4–6°C. Such suspensions, as judged by animal experiments,[4–6] remain viable for at least 24 hours. The marrow-cell suspension may then be given intravenously at a time determined by the excretion of the drug employed. The need for a prolonged period of anæsthesia is thus obviated.

J. G. HUMBLE
K. A. NEWTON
D. E. PEGG.

Westminster Hospital, London, S.W.1.

TRIAL OF A NON-SPECIFIC ANTI-CATARRH VACCINE

SIR,—I have read with interest the letter by Dr. Clark and Dr. Grenville-Mathers (June 25) in which they report their trial of an anti-catarrh stock vaccine, as a prophylactic in patients suffering from recurrent chest infection. The vaccine was given subcutaneously in doses of 0·25, 0·5, and 1 ml. at seven-day intervals, starting in the autumn and continued with 1 ml. doses at monthly intervals until March. They report that under such circumstances the vaccine, as a prophylactic, showed itself quite useless.

This result is so much at variance with similar work of my own, using a similar stock vaccine (Parke Davis anti-catarrh) that I should like to put on record my procedure in the use of such a vaccine, wherein I have found it eminently successful in like patients in eliminating recurrent winter bronchitis.

The only difference between our respective procedures is that I employ smaller vaccine doses, on the supposition that, in recurrent bronchitic chest infection, whether the condition is accompanied or not by asthma, one is up against an allergic state of affairs, requiring a very much smaller dose of vaccine. The dose I usually employ is an initial 0·05 ml. subcutaneously, which, if well supported, is followed in the succeeding weeks with 0·1, 0·15, 0·2, 0·25, up to 0·35 ml.; and thereafter, with a sustaining "booster" dose, fortnightly to begin with, and later once a month, of 0·15–0·2 ml. If during the course of the initial series of six, or more, doses, there is any noteworthy *local* reaction after any particular dose, I do not increase the dose at the next weekly date, but give the same dose over again, and in the weeks that follow continue cautiously with increasing doses until eventually a dose of 0·35 ml. is reached. The immunity thus attained is thereafter maintained at a high level by the "booster". The course, when it has served its purpose, is suspended, until just before the following winter when it is begun afresh.

Incidentally, for years I have been recommending this same scheme of dosage, &c., for prophylaxis against ordinary colds, the usual forerunner of bronchitis.

A word of warning: I do not recommend putting the foregoing scheme of dosage into operation other than as a prophylactic, because of the risk of undesirable *focal* reactions in the presence of active bronchitis.

To summarise: the fact that it is possible to control bronchitis prophylactically by the injection of repeated small doses of a vaccine, composed of respiratory bacteria, suggests that it is highly probable that the bronchitic condition is of allergic nature; and, therefore, calls for much smaller doses of vaccine than those employed in the "trial" of Dr. Clark and Dr. Grenville-Mathers.

Wright-Fleming Institute, St. Mary's Hospital, London, W.2. ARTHUR COMPTON.

PNEUMONIA WITH ANTIBODIES TO STREPTOCOCCUS M.G.

SIR,—I have read with interest the article of June 25 by Dr. Anderson. He states that "in general practice, the study of atypical pneumonia must depend on the finding of *Streptococcus* M.G. antibodies, as the testing for cold-agglutinins presents technical hazards which are difficult to overcome". This statement is certainly true if the presence of increased cold agglutinins is tested for by titration. Not only is this method time-consuming, but the titre obtained is subject to many variables which may make the findings in an individual case difficult to interpret.

In 1958 I described [1] a simple and rapid test for the presence of increased cold agglutinins. This test takes less than one minute to perform and requires only a few drops of whole blood. Its practical value has been confirmed by Sterner and Peterson in Stockholm,[2] and it has been a routine laboratory procedure at the Victoria Hospital for Children, Chelsea, for the past two years. Its regular use by myself over a number of years has shown that not only was there an epidemic of virus pneumonia in 1954 [3] but also in 1958 [4] when 49 cases were diagnosed at this hospital alone.

Victoria Hospital for Children, Chelsea, London, S.W.3. D. H. GARROW.

TIGLOIDINE

SIR,—A certain amount of attention has been focused on this minor alkaloid of the atropine series by the recent report [5] of its successful use in the treatment of spastic paraplegia. As manufacturers of the drug, we feel that an outline of its history and present status may be of interest to some of your readers.

Tigloidine was first isolated from *Duboisia myoporoides* in these laboratories about 1937, and its synthesis was reported shortly afterwards by Barger et al.[6] Its pharmacology was subsequently studied by Trautner and McCallum and in 1951 it was suggested [7] that tigloidine might be useful in parkinsonism. Later Trautner and Gershon [8] reported useful activity also in Huntington's chorea. Clinical investigations in this country failed, however, to substantiate the claims for

1. Begg, A. C. *Brit. J. Radiol.* 1954, **28**, 318.
2. Lester, J., Lampe, C. E. *ibid.* 1957, **30**, 145.
3. McFarland, W., Granville, N. B., Dameshek, W. *Blood*, 1959, **14**, 503.
4. Billen, D. *Nature, Lond.* 1957, **179**, 574.
5. Billen, D. *J. nat. Cancer Inst.* 1959, **23**, 1989.
6. Mannick, J. A., Lochte, H. L., Thomas, E. D., Ferrebee, J. W. *Blood*, 1960, **15**, 517.

1. Garrow, D. H. *Brit. med. J.* 1958, ii, 206.
2. Sterner, G., Peterson, N. *Svenska Läkartidn.* 1959, **56**, 2246.
3. Garrow, D. H. *Proc. R. Soc. Med.* 1955, **48**, 841.
4. *ibid.* 1959, **52**, 641.
5. O'Rourke, F. J., Gershon, S., Trautner, E. M., Shaw, F. H. *Med. J. Aust.* 1960, i, 73.
6. Barger, G., Martin, W. F., Mitchell, W. *J. chem. Soc.* 1937, ii, 1820.
7. Trautner, E. M., Noack, C. H. *Med. J. Aust.* 1951, ii, 751.
8. Trautner, E. M., Gershon, S. *Aust. Ann. Med.* 1958, **7**, 286.

tigloidine in parkinsonism, and although we have continued to synthesise it from time to time in small quantities, we have not considered it worth exploring further its possible clinical uses.

O'Rourke's paper has again raised the question of whether tigloidine has a real and useful place in the treatment of organic disease of the central nervous system and there have been a number of inquiries about the availability of the drug. In view of the generally disappointing results which have been reported in the past with drugs for the relief of spasticity we feel that we should not market tigloidine until we have satisfied ourselves, by means of controlled clinical investigations, that the Australian results are reproducible in this country. As tigloidine, in the doses recommended by O'Rourke, is a comparatively expensive drug and large quantities are not at present available, we have decided to limit supplies for the time being to centres with facilities for carrying out controlled trials.

Tablets, each containing 100 mg. tigloidine hydrobromide, and matching dummy tablets will shortly be available, free of charge, and clinicians wishing to conduct a controlled trial of this drug are invited to write to us giving an outline of the proposed trial and an estimate of their requirements of tablets and dummies.

Duncan Flockhart Research Laboratories,
Blandfield Chemical Works,
Edinburgh, 11. W. T. SIMPSON.

ESTIMATION OF HUMAN CHORIONIC GONADOTROPHIN IN BIOLOGICAL FLUIDS BY COMPLEMENT FIXATION

SIR,—An in-vitro procedure for the determination of human chorionic gonadotrophin (H.C.G.) has long been a desideratum. At present both qualitative and quantitative estimations are carried out with biological methods.

The basic thought underlying the present investigation is that the determination of this hormone might be made by means of an antigen-antibody reaction. The estimation of human growth hormone by an immunological technique, using sera from hyperimmunised rabbits, has been described.[1] Previous investigations suggest that pituitary gonadotrophins also exert certain antigenic effects in animals of other species.[2–4] To the best of our knowledge studies on the antigenic properties of H.C.G. have not been published. This is a preliminary report of attempts to induce the formation of antibodies against H.C.G. and to estimate H.C.G. in biological fluids with an immunological method.

Rabbits were immunised with H.C.G. prepared according to Claesson, Högberg, Rosenberg, and Westman[5] (Gonadex-Leo, kindly supplied through the courtesy of Dr. Högberg, AB Leo, Hälsingborg, Sweden). This is a crystalline and electrophoretically homogenous preparation of the hormone from urine of pregnant women. On day 1 the animals received 600 I.U. of H.C.G. in 1 ml. of saline intraperitoneally. At the same time and on five further occasions at intervals of one to two months 2 ml. of an H.C.G.—adjuvant mixture (10 parts H.C.G.-solution, 9 parts paraffin oil, and 1 part Arlacel A) were given subcutaneously. The H.C.G. content of the inoculum was 600 I.U. the first three times, thereafter 1200, 6000, and 9000 I.U. Control rabbits were inoculated with saline and adjuvant.

Blood was drawn before the inoculations were started and at various intervals, usually one to three weeks after each inoculation. Serum was separated, heated at 56°C. for 30 minutes, and stored at −20°C.

TABLE I—"BOX TITRATION" OF H.C.G. WITH SERUM FROM AN H.C.G.-IMMUNISED RABBIT

Antigen	Dilution of antigen	Dilution of antiserum				
		8	16	32	64	128
H.C.G. 3000 I.U. per ml.	2	−	−	−	−	−
	4	+	−	−	−	−
	8	+	+	−	−	−
	16	+	+	−	−	−
	32	+	+	+	−	−
	64	+	+	+	+	−
	128	+	+	+	+	−
	256	−	−	−	−	−

The gel-diffusion precipitation test [6] was applied to ascertain the possible presence of antibodies against H.C.G. in rabbit sera. Repeated attempts have yielded no positive results to date.

Next the complement-fixation (C.F.) test was tried. In this investigation the plate test of Fulton and Dumbell [7] as used by Svedmyr, Enders, and Holloway [8] was employed. A "box titration" of H.C.G.-solution with rabbit antiserum is shown in table I. The results indicate the presence of C.F. antibodies in the rabbit serum. In this experiment the highest antigen dilution giving optimal serum titre was 1/128. This corresponds to 24 I.U. of H.C.G. per ml. Heating of the antigen-solution at 56°C for 60 minutes prior to the test did not change the result. Simultaneous titrations of control rabbit serum with H.C.G. were negative.

In order to investigate the clinical application of this method, sera, and urine specimens from pregnant women as well as from non-pregnant subjects of fertile age were examined. All specimens had been heated at 56°C for 60 minutes. The samples were tested in "box titrations" for the presence of antigen reacting with the rabbit serum. Initial studies revealed differences in the C.F. capacity of specimens from pregnant and non-pregnant subjects.

Most samples from non-pregnant individuals, however, also fixed complement, although with a distinct prozone. This apparently non-specific reaction could be overcome by the admixture of an equal amount of serum from non-pregnant women to the rabbit hyperimmune serum. Details will be given later.

TABLE II—COMPLEMENT-FIXATION TESTS ON HUMAN SERA AND URINE SAMPLES FROM PREGNANT WOMEN WITH SERUM FROM AN H.C.G.-IMMUNISED RABBIT

Duration of pregnancy (month)	Specimen	Reciprocal of highest specimen dilution giving optimal serum titre
2nd (imminent abortion)	Serum	8
2nd (normal pregnancy)	"	64
3rd	"	64
5th	"	16
5th	"	16
4th (hydatidiform mole)	"	256
2nd (imminent abortion)	Urine	4
3rd (normal pregnancy)	"	16
4th (hydatidiform mole)	"	256

With this modification of the technique eleven specimens from non-pregnant individuals so far tested (eight sera and three urine samples) did not show any C.F. reaction with the rabbit hyperimmune sera, whereas the results with nine specimens from pregnant women all were positive (table II).

Investigations are now in progress on the sensitivity, specificity, and accuracy of this procedure for the determination of H.C.G. and to ascertain the application of this method as a pregnancy test. These investigations will be published elsewhere.

Department of Women's Diseases,
Karolinska Sjukhuset,
Stockholm. SAM BRODY.

Virus Department of the Central
Bacteriological Laboratory of Stockholm City
and Department of Virus Research,
Karolinska Institutet, Stockholm. GUN CARLSTRÖM.

1. Read, C. H., Stone, D. B. *A.M.A. J. Dis. Child.* 1958, **96**, 538.
2. Meyer, R. K., Wolfe, H. R. *J. Immunol.* 1939, **37**, 91.
3. Thomspon, K. W., Melnick, J. L. *Endocrinology*, 1941, **28**, 723.
4. Deutsch, H. F., McShan, W. H., Ely, C. A., Meyer, R. K. *Amer. J. Physiol.* 1950 **162**, 393.
5. Claesson, L., Högberg, B., Rosenberg, Th., Westman, A. *Acta endocr., Kbh.* 1948, **1**, 1.
6. Ouchterlony, O. *Acta path. microbiol. scand.* 1948, **25**, 186.
7. Fulton, F., Dumbell, J. R. *J. gen. Microbiol.* 1949, **3**, 97.
8. Svedmyr, A., Enders, J. F., Holloway, A. *Proc. Soc. exp. Biol., N.Y.* 1952, **79**, 296.

PAY INCREASE TO MEDICAL SUPERINTENDENTS

SIR,—Dr. Oldham (June 25) and Dr. Gilsenan (July 2) do well to draw the attention of the profession to the inappropriateness of the proposed increase of £250 per annum to medical superintendents of mental hospitals. One can only assume that the Pilkington Commission, in making the recommendation, had in mind the National Health Service (Superintendents of Mental Hospitals, etc.) Regulations, 1948, which made the superintendent the chief officer of the hospital and responsible for its general management. Since the Minister of Health recently decided to revoke these regulations on the coming into force of the main provisions of the Mental Health Act, 1959, any justification that may possibly have existed in the past for the proposed additional payment to superintendents no longer does so. In future the responsibility of a medical superintendent of a mental hospital, if the post is retained, will be neither greater nor less than that of his fellow consultants. There would therefore appear to be no grounds for implementing this particular recommendation of the Pilkington Commission.

Scalebor Park,
Burley-in-Wharfedale,
near Leeds. CHARLES P. GORE.

SIR,—A fear often expressed is that with the new outlook on mental illness and the changes that are occurring as a result, medical administration will tend to fall more and more into the hands of lay administrators. It is argued, for example, that a permanent medical administrator is necessary for the administration of ancillary staff. There is, though, no reason why the day-to-day medical administration necessary in mental hospitals in the future should not be able to be carried out eventually without extra pay by the elected chairman of the medical staff committee. This position usually rotates among senior staff and such an arrangement has many advantages.

Norton Fitzwarren,
Taunton. MARTIN F. BETHELL.

THE TURN OF THE TIDE

SIR,—For some time many public-health dentists have felt that the chance of ever affording full comprehensive dental treatment to all patients is gradually vanishing because there are so few dentists to do the work. Meanwhile dental decay is steadily increasing, and a new approach to public-health dentistry is needed. By placing the emphasis on dental prevention and dental-health education, rather than treatment, it may be possible to achieve a far greater measure of improvement in dental health. New prospects in preventive dentistry have been opened up by the discovery that the ingestion by children of fluoridated water gives considerable protection against dental caries. It may be possible to offer the same protection to children not living in an area with a fluoridated water-supply by the topical treatment of the dentition with certain fluoride salts of predetermined concentration.

The addition of fluoride to deficient public water-supplies reduces the incidence of dental caries by up to 60% when the fluoridated water has been ingested from birth. The number of man-hours of dental treatment that could be thus saved by a widespread fluoridation programme would be almost incalculable.

Of the fluoride salts that may be used for topical application 8% stannous fluoride seems best, as demonstrated by Muhler, of Indiana University. It seems to give considerable protection, and one application, properly made, is usually sufficient. The fluoride preparation should be prepared freshly for each application so that the stannous tin is in an active state. A simple method is as follows:

0·8 g. of the salt is made up in no. 0 gelatin capsules and the capsules kept in an airtight tin or jar. To make up each individual fresh preparation, the contents of a capsule are added to 10 ml. of distilled water, thus making sufficient 8% solution to treat one patient. After detailed prophylaxis, the teeth are thoroughly dried, and the fresh solution is applied with a little cotton-wool. One quadrant of the mouth should be treated at a time, and the teeth kept moist with fluoride for four minutes by regular applications. During the treatment, the teeth are isolated from the tissue by the use of cotton-wool rolls so that no saliva comes into contact with the solution. The patient is then instructed not to eat or drink for half an hour. One such application is usually sufficient, but in those cases where the patient is highly susceptible to caries, a further treatment may be carried out after a short time.

The exact chemical action on the tooth enamel is unknown, but the fluoride seems to have a strong affinity for the enamel constituent. Increased resistance to caries is apparent even when fluoridated water has been and is being taken by the patient.

The best method by far of dental health education seems to be the personal lecture and demonstration with visual aids, such as coloured film-strips. Moving pictures were found to be less satisfactory for teaching schoolchildren than film-strips with personal lecture demonstrations.

Public Health Department,
Tullamore, Offaly, Eire. FRANCIS M. O'CARROLL.

ORAL HYPOGLYCÆMIC AGENTS

SIR,—Dr. Oakley and Dr. Jackson's letter of May 14 in defence of chlorpropamide cites Graham's report of jaundice in a diabetic clinic long before the introduction of oral hypoglycæmia agents. The jaundice occurred only in the hospital patients and Dr. Graham concluded that it must have been due to an infective agent passed from patient to patient at the hospital. Syringes were sterilised by a mixture of methylated spirits and lysol which is of course ineffective against the virus of hepatitis.

New Haven, Connecticut. PAUL H. LAVIETES.

A FERTILE FEMALE WITH XO SEX CHROMOSOME CONSTITUTION

SIR,—We have recently had the opportunity of examining a chromatin-negative female who has given birth to a son.

The patient was born in 1921; she is of short stature (height 136 cm.) but shows no other clinical stigmata of Turner's syndrome. Her breasts are very well developed and she has normal axillary and pubic hair. Her menarche occurred in her 16th year and she is still menstruating regularly at 5-week intervals. At the age of 31 she gave birth to an apparently normal boy who, on subsequent clinical examination, showed no abnormality and was found to be chromatin-negative. There is no doubt that the woman is the mother of the boy as the records of the delivery, which took place in a maternity hospital, are still available; the appearance of the cervix on recent examination is compatible with her having borne a child; and full blood-group studies on both mother and child revealed no inconsistency.

The cells of the skin and buccal mucosa of the mother are chromatin-negative and she has no " drumsticks " on her polymorphonuclear leucocytes. Chromosome studies were carried out on cultures of skin and bone-marrow:

	Total cells	*<44*	*44*	*45*	*46*
Skin (D. G. H.)	25	0	0	24	1
Bone-marrow (P. A. J.)	45	3	2	36	4
Bone-marrow (K. W.)	22	3	1	15	3

The majority of the cells have 45 chromosomes and all those analysed are consistent with an XO sex chromosome constitution. Analysis of the cells with counts differing from 45 suggested that these are artefacts which had arisen during preparation. None of the cells with a count of 46 could be inter-

preted as having a normal female chromosome complement. We have, therefore, no evidence to suggest that this patient is a chromosome mosaic.

Hoffenberg et al.[1] and Stewart [2] have reported chromatin-negative cases of Turner's syndrome who had menstruated over a period of several years. These cases may have been fertile but the present case is the first chromatin-negative female in whom fertility has been proved. Such cases illustrate the variability of the phenotype which can be associated with an XO sex chromosome constitution.

F. BAHNER
G. SCHWARZ.
Medizinische Poliklinik, University of Heidelberg, Germany.
D. G. HARNDEN
M.R.C. Group for Research on the General Effects of Radiation, Western General Hospital, Edinburgh.
P. A. JACOBS.
Department of Pathology, University of Heidelberg, Germany.
H. A. HIENZ.
Medizinische Universitatsklinik, University of Heidelberg, Germany.
K. WALTER.

CONFIRMATORY MEDICAL CERTIFICATE BEFORE CREMATION

SIR,—I am grateful to my colleagues who have taken the trouble to comment on my original letter, and should like to deal with some of the points raised.

I think it would not be suitable for a person who did not witness the postmortem to sign the confirmatory certificate; I don't think it would be adequate merely to talk to the man who performed it. It would be a way out of the difficulty, if attending the necropsy authorised the witness to answer "yes" to the question "did you make a postmortem examination"—but I understand this is not the case.

I entirely agree that the pathologist has a good claim to sign the confirmatory certificate; in fact, if nobody attends at his postmortem examination, I consider he is the only one who should do so. But sometimes he may not sign because he does not satisfy the necessary conditions. In this hospital, our pathologist has generously agreed to waive his claim in favour of the relevant registrar (provided he attends the necropsy). How should the question be answered then? I feel it would be much better if the form were designed to elicit the desired information: Was a postmortem examination performed? Are you aware of the findings?

Whipps Cross Hospital, London, E.11.
E. HINDEN.

SELECTION OF BREAST-CANCER PATIENTS FOR ADRENALECTOMY AND HYPOPHYSECTOMY

SIR,—In his letter of June 11, Dr. Nabarro suggests that the ratio of the urinary 17-hydroxycorticosteroids (17-OHCS) to ætiocholanolone (which we found correlated with response to hypophysectomy) is merely an index of the "general condition" of the patient. He suggests that the ratio of 17-OHCS/ætiocholanolone is high in seriously ill, debilitated subjects and low in patients whose condition is well maintained.

We do not believe that a method exists for selecting patients for hypophysectomy on the basis of their "general condition". In our series an independent observer initially rejected only those very few patients he thought unfit to withstand an operation. Approximately a third of the remainder could be classified subjectively as "very ill". No correlation could be found between the above ratio of urinary steroids and the patient's condition according to this classification. Furthermore the classification bore no relation to their subsequent response to operation. Whereas 40% of the very sick patients responded well to treatment, 50% apparently fit patients failed to benefit.

We appreciate that an attempt to classify patients according to their general health is very inexact. After a careful perusal of our case-records, however, we see no reason for pursuing a hypothesis which from our figures derives no support.

H. J. B. ATKINS
R. D. BULBROOK
M. A. FALCONER
F. C. GREENWOOD
J. L. HAYWARD
K. S. MACLEAN
P. SCHURR
Guy's Hospital, London, S.E.1.
P. ARMITAGE.

ORNITHOSIS IN RAILWAY GUARDS

SIR,—This is probably a more common industrial hazard than the two cases reported by Dr. Dew and his colleagues (July 2) suggest. In October, 1954, I saw a man of 63 during a febrile illness with cough, which would clinically have fitted with the diagnosis of psittacosis. The Virus Reference Laboratory reported a titre of 1/32 in his serum. He at first denied contact with or interest in birds, but when pressed as to his occupation remembered that as a railway guard he carried a large number of pigeons at least once a week.

Kingston Hospital, Kingston upon Thames, Surrey.
D. STARK MURRAY.

THE HARVEST MITE

SIR,—Has Dr. Roantree (July 2) any evidence for his statement that probably "a substantial percentage of the human population is . . . not attacked at all" by harvest mites? Different men, women, and children may show slight differences in their attractiveness to biting insects and mites, but I have never found anyone who is so repulsive as not to be bitten at all. Great differences in the reaction to bites are found, and the same person may become more or less seriously affected, depending on his previous exposure to any particular species.[1]

Protection from biting mites, as you have stated, is simple. A small quantity (about 1 ml.) of dimethyl phthalate, dibutyl phthalate, or benzyl benzoate smeared on the socks will give protection to those who only walk through infested areas, and this protection persists even when the socks are washed. Those who lie down, for whatever reasons, in infested vegetation, offer more scope to the mites, and it might be worth showing the film which I made during the war to help in the training of troops entering areas in S.E. Asia where mite-borne typhus was a danger. This was based on the methods devised by Australian scientists in New Guinea for treating all the garments of those at risk. Scantily clad holiday-makers are fortunate as mites seem to bite only where some garment, garter, belt, or the like, constricts the skin, and if the fabric of this region is smeared with benzyl benzoate or other poison good protection is obtained (though if applied too liberally some synthetic fabrics are dissolved with possibly embarrassing results).

Rothamsted Experimental Station, Harpenden, Herts.
KENNETH MELLANBY.

SIR,—Your leading article on this subject was most timely. There are two points of interest about trombiculosis which were not mentioned. It would be interesting to know whether entomologists agree with the common view that the most severe nuisance from mite bites always occurs on chalk soils.

There is a radical treatment, personally practised for twenty years, which is somewhat painful but effective. The hard, itching papules are squeezed, one by one,

1. Hoffenberg, R., Jackson, W. P. U., Muller, W. H. *Proc. nat. Acad. Sci., Wash.* 1959, **45**, 560.
2. Stewart, J. S. S. *Acta endocr., Copenhagen*, 1960, **33**, 89.

1. Mellanby, K. *Nature, Lond.* 1946, **158**, 554, 750.

between the two thumb nails until they burst and a slight show of blood appears. This treatment is best performed, with or without help from an assistant, in the bath. Itching ceases for good, and rare recurrences can be retreated. I have never found topical applications effective for more than an hour or two, but after half an hour's work on an anguished patient with fifty or sixty bites, he can be confident of cure.

M.R.C. Group for Research in Bilharzia, St. Albans, Herts. J. NEWSOME.

BEDSORES OF THE GUT

SIR,—I have read with great interest in your issue of June 25 the excellent leading article, which ends by asking two questions:

"Should we not consider whether the withholding of food by mouth from ill, shocked, semicomatose, and comatose patients does not needlessly expose their gut mucosa to severe chemical irritation? Intravenous therapy can provide water, salt, and calories; but it cannot neutralise or dilute gastrointestinal enzymes, nor stimulate peristalsis. Was there some sense after all in that much-maligned cup of hot sweet tea?"

Dalgaard,[1] whom you quote, considers that the close association between certain types of cerebral lesions and acute peptic ulceration as a mere chance coincidence can be excluded. He quotes Baló who made the significant observation that within a very short time a few ulcers appeared to be already in process of healing and that it is reasonable to assume that the acute ulcers might have healed if the patients had survived the primary cerebral lesion.

I believe that it is now generally admitted that the acute lesion is, invariably and characteristically, *symptom-free* in contradistinction to the *painful* chronic lesions and that the former, which cannot be diagnosed clinically except when it is complicated by hæmorrhage or perforation, originates in the *submucosa*, while the latter originates in the *mucosa*. Indeed, the acute and chronic lesions are two unrelated disease entities.

Since in the shocked patient the gastric secretions are considerably reduced and since, in any case, the acid element does not participate in the causation or maintenance of the acute ulcer, there is no reason further to reduce gastric acidity. I have stated on many occasions that the acute lesion is a secondary manifestation of a remotely situated pathological focus; it represents the "alarm reaction" of Selye, who advocates the administration of glucose as the appropriate treatment.

These considerations suggest the answer to both questions. The answer to the first must be in the negative and to the second in the affirmative.

More detailed information on this subject may be found in my monograph *Gastro-Duodenal Ulcer*.

J.-JACQUES SPIRA.

"PSYCHOTHERAPEUTIC"

SIR,—Recent years have seen the introduction of a number of effective drugs which by their influence on various central neurophysiological mechanisms are of value in the treatment of certain mental and nervous disorders.

The makers of a new such product, which is claimed to be specific for the relief of anxiety and tension, introduce it as a "psychotherapeutic". This misnomer calls for correction before it becomes established—leaving aside the question of whether this (or an analogous drug) is effective or not. Psychotherapy (and its adjective, psychotherapeutic) have long been established as referring specifically to non-physical methods of effecting change in a patient, and to describe a chemical agent as psychotherapeutic is therefore a mistake. But it is a matter of much more than a misnomer, for this usage carries an implication of the chemical *causality* of psychic processes.

The Middlesex Hospital, London, W.1. ALEXANDER DUDDINGTON.

1. Dalgaard, J. B. *A.M.A. Arch. Path.* 1960, **28**, 359.

BLOOD-TRANSFUSIONS FOR DENTAL EXTRACTIONS IN HÆMOPHILIA

SIR,—Following publication [1] of the method used for dental extractions in hæmophilia and Christmas disease, I received inquiries regarding the amount of blood given to each patient. May I be allowed to supply this information?

A total of 458 fresh-blood transfusions were used for the successful performance of 92 operations. With the exception of 2 patients who received 11 and 15 fresh-blood transfusions for the extraction of 16 and 6 teeth respectively, no more than 10 fresh blood-transfusions were required for achieving the necessary hæmostasis. Details of the remaining 90 occasions are given in the accompanying table.

TRANSFUSIONS USED FOR TEETH EXTRACTIONS IN HÆMOPHILIA AND CHRISTMAS DISEASE

No. of teeth extracted at each operation	Transfusions of fresh blood* required on each occasion									
	1	2	3	4	5	6	7	8	9	10
	No. of dental operations									
1	3	2	4	6	3	4	3	..	..	..
2	2	4	2	1	1	..	..	..	..	..
3	..	2	1	2	..	..	..	..	..	..
4	1	..	2	3	2	..	3	..	..	1
5	..	..	2	..	1	1	3	2	..	..
6	..	..	..	..	3	..	..	..	..	2
7	..	1	..	1	..	..	..	..	..	..
8	..	..	..	1	1	2	..	1	..	1
9	..	..	..	..	..	2	..	..	..	..
11	..	..	..	1	..	..	1	..	..	..
12	..	..	1	..	..	..	..	..	..	..
13	..	..	..	1	1	..	..	..	..	..
14	..	..	..	1	..	..	..	..	1	..
16	..	..	1	..	..	..	..	..	..	..
17	..	..	..	..	..	1	..	..	..	..
19	..	..	..	..	..	..	..	..	1	..
20	..	..	..	1	..	..	..	..	1	..
25	..	..	..	..	..	..	..	1	..	..
28	..	..	..	..	..	..	..	1	..	..

* Each transfusion consisted of 540 ml. ACD blood or plasma therefrom.

Only after 14 operations did I supplement the fresh blood with packed red cells (5 transfusions) or stored blood (32 transfusions), in order to correct reduction in hæmoglobin levels. Although the condition of 1 of these patients, who had 6 teeth removed, necessitated the use of 10 stored-blood transfusions, the postoperative loss of blood in the remaining 13 operations was adequately replaced by the administration of 1–3 transfusions in each case.

Blood Transfusion Centre, Brentwood, Essex. F. NOUR-ELDIN.

THE MEDICAL DIRECTORY

The Editor of *The Medical Directory* writes:

"The annual schedule, upon the return of which the accuracy of *The Medical Directory* mainly depends, has recently been posted to all traceable members of the medical profession, and its speedy return would be appreciated. A number of schedules, sent to a doctor's last known address, have been returned through the post office marked 'gone away'. Although in such cases every effort is made to find a new address, I should like to remind practitioners that if these efforts are not successful before the book goes to press, the names in question will be omitted from the next edition.

"Any doctor who has not received the annual schedule, or who has mislaid it and would like a duplicate, is requested to communicate as soon as possible with the Editor, *The Medical Directory*, 104, Gloucester Place, London, W.1. The full name and year of qualification of the doctor should be sent for identification."

1. MacIntyre, H., Nour-Eldin, F., Israels, M. C. G., Wilkinson, J. F. *Lancet*, 1959, ii, 642.

Medicine and the Law

Jury's Responsibility in Assessing Diminished Responsibility

A YOUNG man was charged with the murder of a young woman whom he had strangled and whose dead body he mutilated. The killing was admitted; the defence was that he was suffering from diminished responsibility as defined by section 2 of the Homicide Act, 1957.

The uncontradicted defence evidence of the senior medical officer at Birmingham prison and two specialists in psychological medicine was that he was a sexual psychopath with abnormality of mind arising from arrested or retarded development of mind or inherent causes, and that a sexual psychopath with violent perverted sexual desires, which he found difficult or impossible to control, might be normal save when under the influence of those desires. The doctors were of opinion that the killing was done under the influence of perverted sexual desires and that, although not insane in the technical sense laid down in the McNaughten rules, the accused's sexual psychopathy could properly be described as partial insanity. The judge directed the jury that if they came to the conclusion that (1) from an early age the accused had been subject to these perverted violent desires and in some cases had indulged his desires; (2) the impulse or urge of these desires was stronger than the normal impulse or urge of sex to such an extent that the subject found it very difficult or perhaps impossible in some case to resist putting the desire into practice; (3) the act of killing was done under such an impulse or urge; and (4) that setting aside these sexual addictions and practices, this man was normal in every other respect those facts alone would not constitute such abnormality of mind as substantially to impair a man's responsibility for his acts within section 2.

The accused was convicted of murder and sentenced to life imprisonment. He appealed on the ground that that direction, taken as a whole, involved a misconstruction of the section.

The LORD CHIEF JUSTICE, said that the abnormality of mind in section 2(1) of the Homicide Act, 1957, to be contrasted with " defect in reason " in the McNaughten rules, meant a state of mind so different from that of ordinary human beings that the reasonable man would term it abnormal. It was wide enough to cover the mind's activities in all its aspects, including the ability to exercise will-power to control physical acts in accordance with rational judgment. Whether the accused was at the time of the killing suffering from any " abnormality of mind " in that broad sense was a question for the jury. On that question medical evidence was no doubt of importance, but the jury were entitled to take into consideration all the evidence including the acts or statements of the accused and his demeanour. They were not bound to accept the medical evidence if there was other material which conflicted with it and outweighed it. The ætiology of the abnormality of mind did, however, seem to be a matter to be determined on expert evidence.

The crucial question whether the abnormality of mind was such as substantially impaired his mental responsibility for his acts in doing the killing, was one of degree and essentially one for the jury. Medical evidence was relevant, but it involved a decision whether the impairment of mental responsibility was " substantial ", a matter on which juries might legitimately differ from doctors. Furthermore, where the abnormality of mind was one which affected self-control, the step between " he did not resist his impulse " and " he could not resist his impulse " was, as the evidence in this case showed, incapable of scientific proof. There was no scientific measurement of the degree of difficulty which an abnormal person found in controlling his impulses. Those problems which in the present state of medical knowledge were scientifically insoluble the jury could only approach in a broad common-sense way. The court had repeatedly approved directions to the jury which indicated that such abnormality as " substantially impaired his mental responsibility " involved a mental state which a jury would regard as amounting to partial insanity or being on the borderline of insanity.

The court thought that the judge's direction to the jury involved a wrong construction of section 2. Inability to exercise will-power to control physical acts, provided that it was due to abnormality of mind from one of the causes specified in section 2(1), was sufficient to entitle the accused to the benefit of the section; difficulty in controlling his physical acts, depending on the degree of difficulty, might be. It was for the jury to decide on the whole of the evidence whether such inability or difficulty, not as a matter of scientific certainty but on the balance of probabilities, had been established, and in the case of difficulty whether it was so great as to amount in their view to a substantial impairment of the accused's mental responsibility for his acts. The direction in the present case thus withdrew from the jury the essential determination of fact which it was their province to decide. The medical evidence as to ability to control physical acts at the time of the killing was all one way. The revolting circumstances of the killing, the subsequent mutilations, and the previous sexual history pointed, plainly, to the conclusion that the accused was what would be described in ordinary language as on the borderline of insanity or partial insanity. Properly directed, the court did not think that the jury would have come to any other conclusion than that the defence under section 2 was made out.

The appeal would be allowed and a verdict of manslaughter substituted for the verdict of murder. The only possible sentence, having regard to the tendencies of the accused, was imprisonment for life, and the sentence would not be disturbed.

Regina *v.* Byrne.—*Court of Criminal Appeal:* Lord Parker, *C.J.*, Hilbery and Diplock, *JJ.* July 4, 1960. R. K. Brown, Q.C., and John Owen (Registrar, Court of Criminal Appeal); John Hobson, Q.C., and Elizabeth Lane, Q.C. (Director of Public Prosecutions).

C. J. ELLIS
Barrister-at-law.

An Unreasonably Restrictive Covenant

In 1951 the defendant, a Polish medical student, went to live with the plaintiff, a doctor, and his wife, with a view to becoming an assistant to the plaintiff when he passed his examinations. He qualified in April, 1952, and became a trainee assistant to the plaintiff. After nine months he became a salaried assistant, the understanding being that, if things went well, he might expect a partnership after three years. In fact, he became a partner in November, 1953, when the two doctors entered into a partnership agreement for five years. The agreement provided that either party could determine it and contained a covenant that on determination the defendant would not for a period of five years take up general professional practice in a private capacity either on his own account with a medical list or as a partner, assistant, or employee of a general medical practitioner with a medical list within ten miles of the house in Abingdon, Berkshire, from which the partnership practice was carried on.

The partnership deed was drawn up by the plaintiff's solicitors and the plaintiff and his wife explained the clauses to the defendant, but he was not separately advised by a solicitor of his own.

At the date of the deed the patients of the practice numbered about 2275. Only 11 lived outside a five-mile radius from the partnership premises, and, of them, some were only just outside and the others were personal friends of the plaintiff. The other towns of size within the ten-mile radius were Oxford, Didcot, Wallingford, and Wantage.

The defendant determined the partnership in March, 1960. At that time the plaintiff had about 1800 patients on his list and the defendant about 1000. The defendant intended to set up in practice in Abingdon and Drayton about two miles away; and the plaintiff took proceedings for an injunction to restrain him from taking up practice in breach of the covenant. The defendant claimed that the covenant was void as it imposed restrictions in regard to area greater than were necessary for the protection of the plaintiff.

Mr. JUSTICE CROSS said that there was a distinction between covenants between vendor and purchaser and between master and servant.

The court took a broad view of covenants between vendor and purchaser which were generally negotiated at arm's length and on which the parties were often separately advised and did not look too astutely to see whether such covenants were somewhat wider than was necessary. A master was entitled to protect his trade secrets and trade connection after the employment had ended; in some cases it was reasonable that the servant should be restrained from carrying on the same business in a certain area for a certain time, but the court looked at such covenants strictly. In this case, the plaintiff could have determined the agreement at any time, and the defendant would then have been forced to abandon the patients on his list either to the plaintiff or to some other doctor.

When there was a partnership of this sort on these peculiar terms, it was analogous to an agreement between master and servant. The assistant to a doctor was in such a position of confidence that a reasonable area restriction was justified, but it was only justified if it was no more than was strictly necessary. The present covenant went far beyond what was strictly necessary, since there were substantially no patients outside the five-mile radius, and the action must fail. Judgment for the defendant.

O'Connor *v.* Graves-Stanwick—*Chancery Division:* Cross *J.* June 27, 1960. Counsel and solicitors: John Bradburn (Cropley Davies & Son for Walton & Hurd, Marlow); D. A. Thomas (Hempsons).

V. A. MOXON
Barrister-at-law.

Appointments

ANDERSON, D. J. W., M.B. Wales, D.P.H.: assistant M.O. and school M.O., Kingsbridge, Salcombe, and Plympton area.
CARSON, H. E. A., M.D. Lond., D.P.H.: M.O.H., St. Marylebone.
HORSLEY, J. S., M.R.C.S.: senior M.O. (mental health), Sheffield.
JOLLY, H. R., M.D. Cantab., M.R.C.P., D.C.H.: assistant physician, children's department, Charing Cross Hospital, London.
JUKES, MARJORIE V., M.B. Lpool: assistant M.O., Runcorn, Cheshire.
KUNKLER, P. B., M.D. Cantab., M.R.C.P., F.F.R., D.M.R.T.: consultant radiotherapist, Charing Cross Hospital, London.
LYONS, JOSEPH, M.B. Leeds, D.P.H.: deputy M.O.H., West Riding of Yorkshire.
MACDONALD, A. D., M.D. Aberd.: assistant M.O., West Norfolk.
WRIGHT, P. A. C., M.B. Lond., D.P.H.: deputy M.O.H., Tottenham.

The Hospital for Sick Children, Great Ormond Street, London:

COOKE, S. L., M.B. Sydney, F.R.C.S.: house-surgeon.
CRITCHLEY, JANE M., M.B. Lond., assistant M.O., Tadworth Court.
ESMONDE-WHITE, M., M.B.: house-surgeon.
HUNT, M. F., F.R.C.S.: surgical outpatient assistant.
RANSOME-KUTI, OLIKOYE, M.B. Dubl.: M.O., Tadworth Court.

Leeds Regional Hospital Board:

HELM, W. H., M.R.C.P.: consultant physician (general medicine and chest diseases), York and Harrogate areas.
PUGMIRE, S. L., L.R.C.P.I., D.P.M.: consultant in psychiatry and medical superintendent, Wakefield group of mental deficiency hospitals.
WATERS, G. W., M.B. Manc., D.P.M.: consultant in psychiatry and medical superintendent, mental-deficiency group of hospitals, Hull and East Riding areas.

Notes and News

EDINBURGH'S NEW NEUROSURGICAL UNIT

IN Edinburgh neurosurgery as a specialty dates from 1925. Recognition, or at least effective recognition, did not come readily: more than a decade later, neurosurgical patients were scattered through the Royal Infirmary—two here and two there—for lack of a proper unit. That recognition came as quickly as it did was due mainly to the professional skill and the tenacity of Mr. Norman Dott. Recalling earlier trials, Professor Dott must have been gratified when the magnificent new department of neurological surgery at the Western General Hospital, Edinburgh, was opened on July 1 by Mr. J. S. Maclay, Secretary of State for Scotland. Head and spinal-cord injuries continue to be treated at the now highly developed section of the department at ward 20 (22 beds) in the Royal Infirmary. The new section (60 beds) accepts non-traumatic cases.

In the new building patients are accommodated on the first, second, and third floors in ward units of 20 beds each. Each floor has four 4-bed wards and four single rooms. Each of these wards or rooms can be used alternatively for male or female or for child patients. There is more than traditional space for dining-room and lounge, for (in Professor Dott's words) " in these days many patients are able to be up within a day or two of operation, and visiting is increasingly popular—and beneficial ".

On the main roof is a penthouse structure with accommodation for the resident medical staff and sitting-rooms for them and for senior nursing staff.

The ground floor contains the single-storey surgical operating and X-ray suite, clinical laboratories for electroencephalography and special eye examinations, and medical, nursing, and secretarial offices and a staff conference room.

The twin operating-theatres are egg-shaped, to afford smooth air-flow (twenty-one air changes an hour). The air is filtered and conditioned as to temperature and humidity. The air-flow is from the operating and sterilising rooms out through the surrounding ancillary accommodation into a peripheral corridor that acts as an extract duct. Theatre lighting is by heat-filtered projector lights set in the dome-shaped ceiling. The staff changing-room suites are designed so that the staff discard their personal clothes and arrive in the vicinity of the theatre in sterile clothing. There is provision for surgical visitors and students to observe operations at a distance of only twelve feet from the actual field.

The habitable part of the lower ground-floor contains the rehabilitation departments of physiotherapy with hydrotherapy and of occupational therapy.

QUINQUENNIAL REVIEW

THE statutory quinquennial review of the National Insurance scheme has been replaced by a continuous review. The main rates of benefit and contribution were increased in 1955 and again in 1958, and particular benefits have been improved at other times during the period. But the quinquennial procedure has offered the Minister of Pensions and National Insurance an opportunity for consideration of the developments and for an analysis of the present position.[1]

The main rates of pension and benefit now payable are 50*s.* for a single person and 80*s.* for a married couple. With family allowances, a family on benefit now receives 15*s.* a week for each of the first two children and 17*s.* each for any other children; for a widow's children the rates are in each case 5*s.* higher. Since the present rates of benefit were introduced in 1958 the level of retail prices, as measured by the retail prices index, has gone up by about 2%, the equivalent of about 1*s.* on the standard rate of benefit for a single person. In real terms the 40*s.* rate of April, 1955, is equivalent to about 46*s.* 1*d.* at today's price levels, or 3*s.* 11*d.* less than the actual present rate.

The report of the Ministry of Labour and National Service's inquiry into household budgets during 1953 and 1954 showed that families mainly dependent on National Insurance pensions or Assistance spent 41% of their total incomes on food, as against 34% by people within the range covered by the retail prices index. Since the present retail prices index was started

1. Report by the Minister of Pensions and National Insurance on his Quinquennial Review of the Rates and Amounts of National Insurance Benefit. H.M. Stationery Office. 1960. Pp. 6. 6*d.*

at the beginning of 1956, food prices have gone up by 7·3%, against a rise of 10·3% in the index as a whole, while the rates of National Insurance benefits have gone up by about 25%. The survey carried out by the Ministry of Agriculture, Fisheries, and Food showed that the expenditure on food of people mainly dependent on National Insurance pensions or on Assistance rose by about 10% between 1957 and 1959 (from 25*s.* 7*d.* to 28*s.* 2*d.* a week per head), while food prices rose 3% and the expenditure per head for all people covered by the survey went up only by about 4% (from 28*s.* 1*d.* to 29*s.* 3*d.*).

About 1 million pensioners were drawing deferred retirement pensions which were on average some 7*s.* 6*d.* above the standard rate. Beneficiaries with small, or no other, resources and with responsibilities for rent are entitled to apply for supplements from the National Assistance Board. In March, 1960, about 22·5% of retirement pensioners, 14% of sickness beneficiaries, and about 15% of widows were doing so.

The Government Actuary's report on his quinquennial review showed that the cost of National Insurance benefits increased from about £500 million in 1954–55 to about £880 million in 1958–59. The largest item of expenditure was on account of retirement pensions. The number of retirement pensioners rose from 4·32 million in April, 1954, to 5·34 million in April, 1959. In 1954 expenditure on benefits represented 3·3% of the gross national product. The corresponding figure for 1959 was 4·7%. The Government Actuary has pointed out that this growth in expenditure will continue, especially over the next twenty years or so, partly because the number of retirement pensioners is expected to rise to about 8 million and partly because the cost of increments and graduated additions to pensions will increase. At present rates the cost of retirement pensions will rise from about £650 million in 1959–60 to £1066 million in 1981–82; and the total expenditure on National Insurance from £959 million in 1959–60 to £1427 million in 1981–82.

The total weekly contribution for an employed man, including the elements for industrial injuries and the National Health Service, is now 18*s.* 2*d.* of which the man himself pays 9*s.* 11*d.* The yield to the National Insurance Fund of contributions from insured persons and employers increased over the period from about £450 million in 1954–55 to nearly £700 million in 1958–59. Exchequer payments to the National Insurance Fund rose from £71 million in 1954–55 to £163 million in 1958–59. The Government Actuary estimated that under the 1959 Act income and outgo of the National Insurance Fund would broadly be in balance over the years, but that additional contributions would be needed to finance improved standards of benefit.

"DISABLED LIVING"

A CENTRE for studying and advising on the everyday problems of the severely disabled patient living at home will shortly be opened in the grounds of the Nuffield Orthopædic Centre at Oxford. Named the Mary Marlborough Lodge, this "disabled living research unit" has been built by the National Fund for Research into Poliomyelitis and will be directed by Prof. J. Trueta.

There are twelve beds for patients and for the relatives who may come to learn how to help them. Two of the beds are in a small flat, so that a patient and a relative, while still under skilled supervision, can practise life at home.

In the residential wing patients will be able to practise dressing, toilet, bathing, and so on, and to select different aids which they may need at home. In the day wing are a kitchen for the disabled, a utility room, and a work-assessment room where the need for special aids and house modifications can be assessed. Here, too, is a workshop for designing and fitting special aids, including ballbearing feeders and artificial muscles, with a full-time technician specialist in charge.

Though the unit is financed by the Oxford Regional Hospital Board, patients from any hospital region will be accepted. Those disabled by poliomyelitis will have priority, but others with suitable locomotor disabilities will also be taken. They will be admitted for periods varying from a few days to, at most, two or three months, so that they can (1) learn how to live with their disabilities as independently as possible, (2) select the special aids best suited to their needs, and (3) be fitted with the recently developed aids for the severely paralysed.

Inquiries should be addressed either to Dr. Margaret Agerholm or to the warden, Miss Wanda Williams, Mary Marlborough Lodge, Nuffield Orthopædic Centre, Oxford.

EMERGENCY BED SERVICE

LAST year[1] was a quiet one for the service, with 55,847 requests for beds compared with 63,807 during 1958–59. The winter was, indeed, one of the quietest since the start of the National Health Service, and weekly applications for general acute cases rarely rose above 1300. Yet from January to March 11·4% of general cases were admitted by the medical-referee procedure—a figure only fractionally below that for the same period of 1959 (11·6%), when applications were much more numerous. For the past two years the service has been increasingly asked to arrange last-minute admissions for normal maternity cases for social reasons. Usually the family doctor or antenatal clinic have known that a hospital confinement would be necessary, but they have been unable to book a bed in advance, and the service has been asked to deal with the case after the patient has started labour. Since August, 1959, there has been a slight improvement in this situation, and, allowing for seasonal influences, the number of these cases handled by the service has fallen slightly.

University of London

Dr. H. E. de Wardener, reader in medicine at St. Thomas's Hospital Medical School, has been appointed to the chair of medicine at Charing Cross Hospital Medical School.

Dr. de Wardener, who is 44 years of age, was educated at Malvern College. He qualified from St. Thomas's Hospital in 1939 and served with the R.A.M.C. till 1946. For three years he was a prisoner of war in Siam and for his work in the camps he was appointed M.B.E. In 1946 he became an ex-Service registrar at St. Thomas's. After six months as registrar at St. Helier's Hospital he returned to St. Thomas's in 1948 as medical registrar, and the following year he was appointed senior lecturer in medicine at St. Thomas's Hospital Medical School. He became reader in 1959. He was elected F.R.C.P. in 1958. His published work includes a report on cerebral beriberi in a prisoner-of-war camp and papers on renal function and disease.

The title of reader in growth and development of children has been conferred on Dr. J. M. Tanner, in respect of his post at the Institute of Child Health.

The following degrees have been awarded:

M.D.—Patrick O'Gorman, B. L. C. Phillips.
M.S.—F. G. Ellis.

University of Durham

On July 1 the honorary degree of D.SC. was conferred on Dr. Donald Hunter.

University of St. Andrews

On June 28 the honorary degree of LL.D. was conferred on Prof. J. M. Webster.

Also the following degrees were conferred:

M.D.—H. T. Howat (honours and a university gold medal); J. R. Rintoul (high commendation).
Ch.M.—John Grieve.
M.B., *Ch.B.*—M. J. Weiner (honours); Sydney Wain, W. R. Porter, M. G. Barker (commendation); J. F. Agnew, Barbara Ainsworth, P. J. Ashworth, I. C. Baxter, M. M. Besen, Elizabeth A. Blair, Wesley Boodish, T. C. K. Brown, E. A. O. Bucknor, Robert Coulthard, D. J. Cowley, Kenneth Davidson, D. McG. Duncan, E. M. Duncan, Alison M. A. Elder, G. C. Ferguson, J. B. Ford, J. C. Forrester, W. McG. Gardiner, F. J. Gibbins, O. P. Goertz, Jalal Marzuke Haddadin, C. S. Hampton, P. J. Hirsch, A. L. Honeyman, Elizabeth M. Husband, C. M. Iskander, Arthur Kaufman, R. E. Lea, P. W. Leech, John Leslie, Margaret S. R. McEwan, Francis McGrory, L. M. Mackenzie, R. A. S. MacLean, I. G. Mannall, T. G. Napier, T. D. Osafo, D. M. Piercy, Jacques Politi, D. R. Roberts, Elizabeth S. Ross, Derrick Sapsford, Vida A. Skinner, M. McD. Smith, A. G. Stewart, Elizabeth M. Sutherland, Anne Wannop, Joyce M. Watson.

University of Aberdeen

Dr. J. A. M. Findlay has been appointed a lecturer in anatomy and Dr. G. M. Robb an assistant in biological chemistry.

---

1. Report for the year ended March 31, 1960. Obtainable from E.B.S., Fielden House, 28, London Bridge Street, S.E.1.

University of Dublin

On June 30 the following degrees were conferred:

M.D.—Eunice Hurworth, I. J. Temperley.
M.A.O.—J. H. N. Ferris.
M.B., B.Ch., B.A.O.—David Abrahamson, R. C. Barton, Anthony Clements, T. F. Conneen, Margaret B. Darley, James Dolan, D. B. Dunham, Mary E. Elland, D. M. Gabbé, Mariana Goulandris, I. D. Grieve, J. F. A. Harbison, Wendy P. Holmes, Kathleen G. Llewellyn-Jones, Isabella V. Lalsingh, J. N. Lavan, G. C. A. Lemon, Mary S. E. McElroy, W. H. A. MacMahon, D. G. Martin, A. A. P. Meeson, Joy L. Nicholas, C. S. Norman, D. S. Nowlan, R. H. O'Connor, Katharine J. Sheehan, R. C. Simpson, Ian Slater, Edna V. Sleith, S. G. Smith, B. J. Spencer, J. H. Thompson, Alexander Tomkin, R. T. Wales, S. Chinatu Woko.

Royal College of Surgeons in Ireland

On June 24 the licence in midwifery and surgery was conferred on the following:

Angeliki Bianchi, Pauline E. Buckeridge, A. P. Brennan, P. Min Chung Chan, Robert Chen, Moosa Coovadia, Abdulla Ismail Dangor, G. K. Darby, Sheila D. Dervish, S. C. V. Fok, P. D. B. Forsythe, Doom-Raz Gaya, A. H. Goldberg, A. J. Gomes, Lorna A. G. Greene, Joan E. B. Hannigan, A. K. P. Harbison, C. A. Harkin, Nuala M. Hogan, T. G. Hogan, Jadwiga Teresa Iwanowska, Sheila M. Johnson, Fatehalli Cassim Keshavjee, Helen C. R. M. Kilgallen, Kandiah Kumarashwaran, Lor Kai-Hung, Mohammed Saied Mather, W. G. A. Maxwell, F. T. A. C. Murphy, J. V. M. McGrath, Ng Jit Leong, M. I. O'Boyle, G. J. O'Connor, Clare B. Short, Khaled Ali Qasem, Dhun Sorabjee Rustomjee, Kamaludeen Sayed, Selvanayagan Selvendra, H. B. A. Somaratne, Dulcie E. Suleman, Wanda E. Swiecicka, Brigid M. Taaffe, Khim Keng Tan, Tay Beng-Choo, Gloria Lai-Kit Tong, Santosh Kumar Verma, Mary B. P. Whelan, Kwo Wei Yu.

Guy's Hospital Medical School

Sir Charles Dodds will give the Addison lecture on Wednesday, July 13, at 5 P.M., at the school, London Bridge, S.E.1. His subject will be Thomas Addison.

St. Mary's Hospital Medical School, London

Dr. T. B. Quigley, of the Peter Bent Brigham Hospital, Harvard, will give a lecture on Wednesday, July 27, at 5 P.M. at the school. His subject will be ligament rupture at the ankle and knee—lessons learned from the playing-field.

British Empire Cancer Campaign

North of England Council.—Dr. A. Glucksmann will give the Emily Blake lecture on Thursday, July 21, at 8 P.M. at the Royal Victoria Infirmary, Newcastle upon Tyne. He will speak on biological variation and therapeutic results in cancer of the cervix.

College of General Practitioners

Butterworth gold medal.—This award is offered annually for an essay by a member or associate of the college on a subject connected with general practice. The subject of this year's essay is television and health. Further particulars can be had from the college, 41, Cadogan Gardens, London, S.W.3. The closing date for entries is Sept. 17.

Harveian Society of London

The thundery weather withheld the worst of its misdemeanours for this society's annual Buckston Browne and Gray Hill dinner at the Zoological Gardens on June 28, and once again outdoor refreshment and some of the animals provided agreeable premedication before a pleasant evening.

Canon Charles Raven, proposing the toast of The Society, admitted that his early ambition had been to be a surgeon. In maturer years he had come to realise (as women had always known) that scientific method began with gastronomy and not astronomy. Nevertheless, he regarded psychosomatic philosophy as having started with William Harvey—and certainly today Harvey's example should mean more than ever because of his " sense of wholeness of the whole knowable sphere "

Mr. Terence Cawthorne, the president, reviewed the past year's activities, and was happy that membership of the society was now at its highest—having reached 385.

Dr. C. J. Dickinson, the senior secretary, welcomed The Guests and three honorary members of the society—Sir Victor Negus, Sir Geoffrey Keynes, and Dr. Arthur Morris. Lieut.-General Sir Alexander Drummond, in responding, said that he had known Sir George Buckston Browne and Sir Norman Gray Hill. Both were of yeoman stock; neither would tolerate humbug; and they each knew how courtesy should be governed by pleasure in entertaining guests.

At the end of the dinner Mr. A. Dickson Wright presented Mr. W. E. Tucker, the society's former treasurer, with a silver teapot in appreciation of his services.

Nuclear Safety Advisory Committee

Dr. John Loutit and Dr. A. S. McLean have been appointed members of this committee.

European Society of Hæmatology

This society will hold a congress in Vienna from Aug. 28 to Sept. 2, 1961. Further particulars may be had from the secretariat, 8, Frankgasse, Vienna 9.

International Congress of the History of Medicine

This congress will be held in Greece from Sept. 4 to 14. Particulars may be had from the congress secretary, Prof. Dr. Basile Malamos, 54, Homère, Athens, Greece.

Appeal to the Privy Council

Dr. L. E. Gardiner has lodged an appeal with the Judicial Committee of the Privy Council against the decision of the Disciplinary Committee of the General Medical Council to erase his name from the register.

Royal Anthropological Institute of Great Britain and Ireland

The Huxley medal for 1961 has been awarded to Dr. A. E. Mourant. Dr. Mourant will give the Huxley lecture on Nov. 24, 1961.

Oxford Graduates' Medical Club

All graduates of the University of Oxford who have qualified in medicine are eligible to join this club. The club dines twice a year, the winter dinner being held in London and the summer dinner in an Oxford college. Further particulars may be had from Miss Josephine Barnes, 7, Wimpole Street, London, W.1.

St. Peter's Hospital for Stone, London

Speaking at the centenary celebrations of this hospital on June 30 Mr. Derek Walker-Smith, the Minister of Health, said that in the context of the national hospital building programme, the London postgraduate teaching hospitals presented a special problem. They could not be considered apart from their associated institutes, and the Ministry had sought the cooperation of the university in assessing the development plans.

Psychiatric Prison

On July 1 Mr. R. A. Butler, the Home Secretary, laid the foundation stone of the Grendon Psychiatric Prison in Buckinghamshire (*Times*, July 2). The prison, the first in this country designed for the psychological treatment of crime, is to cost more than £1 million and it is hoped that it will be ready in 1962. Medical officers of prisons and borstals are to select the men to be sent to Grendon. The criteria will be, not the type of offence, but symptoms of maladjustment and willingness to cooperate in treatment. The treatment may include chemical and biochemical techniques as well as individual and group psychotherapy.

Midwives' Rules

Amendments to these rules (S.I. no. 1105) include the removal of the distinction between practising as a midwife and acting as a maternity nurse. In the past, midwives who acted only as maternity nurses were not required to attend compulsory refresher courses. A further amendment reduces the minimum lying-in period from 14 to 10 days. Administratively this is the period for which local health authorities are required to provide adequate service of midwives to attend all women in their areas. It does not have any significance as a period during which mothers should be kept in bed. The requirement that a midwife must notify the local supervising authority of each case in which artificial feeding has been adopted has also been removed from the rules.

On Wednesday, July 13, at 5.15 P.M., at the Royal Free Hospital, Gray's Inn Road, London, W.C.1, Dr. J. R. K. Preedy, of Atlanta, Georgia, will speak on œstrogen metabolism in man.

The medical section of the National Tuberculosis Association has changed its name from the American Trudeau Society to the American Thoracic Society.